https://doi.org/10.5664/jcsm.8684

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Incidence of hypertension in obstructive sleep apnea using hypopneas defined by 3 percent oxygen desaturation or arousal but not by only 4 percent oxygen desaturation

Rohit Budhiraja, MD[1]; Sogol Javaheri, MA, MD, MPH[1]; Sairam Parthasarathy, MD[2]; Richard B. Berry, MD[3]; Stuart F. Quan, MD[1,2]

[1]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Department of Medicine, College of Medicine, University of Arizona, Tucson, Arizona; [3]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Florida, Gainesville, Florida

Study Objectives: This analysis determined ~5-year incident hypertension rates using the 2017 American College of Cardiology/American Heart Association blood pressure (BP) guidelines in individuals with obstructive sleep apnea (OSA) with hypopneas defined by a ≥ 3% oxygen desaturation or arousal but not by a hypopnea criterion of ≥ 4% oxygen desaturation (4% only).

Methods: Data were analyzed from participants in the Sleep Heart Health Study exam 2 (n = 1219) who were normotensive (BP ≤ 120/80 mm Hg) at exam 1. The AHI at exam 1 was classified into 4 categories of OSA severity: < 5, 5 ≤ 15, 15 ≤ 30, and ≥ 30 events/h using both the 3% oxygen desaturation or arousal and the 4% only definitions. Three definitions of hypertension—elevated BP (> 120/80 mm Hg), stage 1 (> 130/80 mm Hg), and stage 2 (> 140/90 mm Hg)—were used to determine incidence rates at exam 2.

Results: Five-year follow-up was available for 476 participants classified as having OSA by the 3% oxygen desaturation or arousal criterion but not by the 4% only standard at exam 1. Incident hypertension using American College of Cardiology/American Heart Association–defined BP categories in these discordantly classified individuals were 15% (elevated BP), 15% (stage 1), and 6% (stage 2). Hypertensive medications were used in 4% of participants who were normotensive. The overall incidence rate of at least an elevated BP was 40% (191/476) in those with OSA defined using the 3% oxygen desaturation or arousal criterion but not by the 4% only criterion.

Conclusions: Use of the 4% only hypopnea definition resulted in the failure to identify a significant number of individuals with OSA who eventually developed hypertension and could have benefited from earlier diagnosis and treatment.

Keywords: OSA, hypopnea definition; incident hypertension

Citation: Budhiraja R, Javaheri S, Parthasarathy S, Berry RB, Quan SF. Incidence of hypertension in obstructive sleep apnea using hypopneas defined by 3 percent oxygen desaturation or arousal but not by only 4 percent oxygen desaturation. *J Clin Sleep Med.* 2020;16(10):1753–1760.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The impact of not identifying OSA defined by a hypopnea definition requiring a minimum 3% oxygen desaturation or arousal but not by more stringent standards (hypopneas scored with a minimum 4% oxygen desaturation) remains unclear. This analysis determined the ~5-year incident hypertension rates using the new 2018 American College of Cardiology/American Heart Association blood pressure guidelines in these individuals.

Study Impact: The ~5-year incident hypertension rate was 40% in individuals with OSA defined using the 3% oxygen desaturation or arousal criterion but not the 4% oxygen desaturation criterion. This result suggests that use of the 4% oxygen desaturation hypopnea definition will fail to identify a significant number of individuals with OSA who will ultimately develop hypertension.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder associated with multiple adverse health outcomes. The apnea-hypopnea index (AHI) is the most commonly employed metric used to describe OSA severity. It represents the number of apneas plus hypopneas per hour of total sleep time. Whereas the description of an apnea is well-established, there remains controversy regarding the definition of a hypopnea. American Academy of Sleep Medicine (AASM) guidelines recommend a definition of hypopnea that includes a 30% or greater reduction in airflow associated with either a 3% or greater decrease in oxyhemoglobin saturation or an arousal from sleep.[1] This definition has been shown to be closely associated with the presence of daytime sleepiness.[2] However, it has not met universal acceptance. Many payors in the United States, including the Centers for Medicare & Medicaid Services (CMS), utilize a more stringent definition of hypopnea that requires at least a 4% drop in oxygen saturation to approve reimbursement for OSA therapy. This threshold is based on data from several large cohort studies establishing a relationship between the CMS definition of OSA and cardiovascular outcomes.[3–5]

Notably, OSA is a highly prevalent condition. Moderate to severe OSA, defined using the 4% criterion, is estimated to be present in 13% of men and 6% of women between ages 30–70 years in the United States.[6] The prevalence is significantly higher when using the AASM definition.[7] Utilizing a

more stringent definition of OSA can potentially exclude numerous people who may be at higher risk of adverse outcomes and benefit from OSA therapy. Hence, there exists a need for large studies that specifically assess the outcomes in discordantly classified OSA (patients diagnosed with OSA using the AASM definition but who do not meet the CMS criteria).

Hypertension is a widely studied adverse outcome of OSA.[8–10] Several potential pathophysiological mechanisms such as intermittent hypoxia-reoxygenation, activation of the sympathetic nervous system, and endothelial dysfunction resulting from OSA may underlie this association. Studies have also shown an improvement in blood pressure (BP) with therapy for OSA.[11–14] However, there are only limited data assessing the relationship between OSA and the updated 2017 American Academy of Cardiology and American Heart Association definitions of hypertension.[15] One cross-sectional study showed that OSA as defined using the AASM definition of hypopnea was associated with a greater risk of having hypertension even among patients who did not have OSA as defined by CMS criteria.[16] However, it is unclear whether individuals who are nonhypertensive and are classified with OSA using the AASM definition of hypopnea but who do not have OSA using the CMS definition (CMS-negative OSA) subsequently develop hypertension. The current study utilized data from the Sleep Heart Health Study, a large community-based cohort of primarily middle-aged adults, to assess the relationship between CMS-negative OSA at baseline and incidence of hypertension over a 5-year follow-up period.

METHODS

Participants

The Sleep Heart Health Study was a prospective multicenter cohort study designed to investigate the relationship between OSA and cardiovascular diseases in the United States. The study rationale and design have been published in detail elsewhere.[17] In 1995, recruitment began with an enrollment of 6,441 participants, aged ≥40 years, from several ongoing "parent" cardiovascular and respiratory disease cohorts who were initially assembled between 1976 and 1995.[18] These parent cohorts consisted of the Offspring and the Omni Cohorts of the Framingham Heart Study in Massachusetts; the Hagerstown (Maryland) and Minneapolis (Minnesota) sites of the Atherosclerosis Risk in Communities Study; the Hagerstown (Maryland), Pittsburgh (Pennsylvania), and Sacramento (California) sites of the Cardiovascular Health Study; 3 hypertension cohorts (Clinic, Worksite, and Menopause) in New York City (New York); the Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study (Arizona); and the Strong Heart Study of American Indians in Oklahoma, Arizona, North Dakota, and South Dakota.

Between 1995 and 1997, these participants underwent a sleep evaluation (exam 1) in the home that included full unattended polysomnography to determine whether they had OSA. Approximately 2 years after exam 1, an abbreviated follow-up exam (FU exam) was performed that included BP measurements at all but the Framingham and Minneapolis sites. Between 2000 and 2003, approximately 5 years after exam 1, the sleep evaluation (exam 2) was repeated in 4,586 participants. Consent was subsequently withdrawn by 134 participants from the Arizona cohort of the Strong Heart Study because of sovereignty issues. Hence, analyses were limited to the remaining 4,452 participants. Parent cohort data were used for documentation of age, height, sex, ethnicity, and smoking status. Institutional review boards for human patient research in the respective parent cohorts approved the Sleep Heart Health Study, and informed written consent was obtained from all participants at the time of their recruitment.

Polysomnography and home visit

For both sleep evaluations, participants underwent overnight in-home polysomnograms using the Compumedics Portable PS-2 System (Abbottsville, Victoria, Australia) administered by trained technicians.[19] The home visits were performed by 2-person, mixed-sex teams in visits that lasted 1.5–2 hours. Visits were scheduled to occur within approximately 2 hours of the participant's usual bedtime. At exam 1, a questionnaire was administered to determine the presence of pre-existing cardiovascular disease and stroke. Cardiovascular disease was defined as previous myocardial infarction, coronary artery bypass surgery, coronary angioplasty, or heart failure. Medications were ascertained at the time of the home visit. For all exams, BP was measured manually in triplicate in a seated position after 5 minutes of rest.[20] The average of the second and third measurements was used for this analysis. A digital scale was used to measure body weight. Body mass index (BMI) was calculated as kg/m^2 using body weight measured at each exam and height from the parent study's database.

The Sleep Heart Health Study recording montage for both the initial and follow-up sleep evaluations consisted of electroencephalogram (C4/A1 and C3/A2), right and left electrooculogram, a bipolar submental electromyogram, thoracic and abdominal excursions (using inductive plethysmography bands), airflow (detected by a nasal-oral thermocouple [Protec, Woodinville, Washington]), oximetry (using finger pulse oximetry [Nonin, Minneapolis, Minnesota]), electrocardiogram and heart rate (using a bipolar electrocardiogram lead), body position (using a mercury gauge sensor), and ambient light (on/off, using a light sensor secured to the recording garment). Equipment and sensors were applied and calibrated during the evening home visit by a study-certified technician. In the morning, the equipment and the data, stored in real time on PCMCIA cards, were retrieved and downloaded to the computers of each respective clinical site. The data were locally reviewed and then forwarded to a central reading center (Case Western Reserve University, Cleveland, Ohio). Comprehensive descriptions of the polysomnography scoring and quality-assurance procedures have been previously published.[19,21] In brief, sleep was scored according to guidelines developed by Rechtschaffen and Kales.[22] Strict protocols were maintained to ensure comparability among centers and technicians. Intrascorer and interscorer reliabilities were high.[21]

The AHI was calculated for each participant using 2 definitions of hypopnea: the AASM recommended definition (3%A) and the AASM acceptable definition (4% only); the latter is the

definition required by CMS. For 3%A, hypopneas were identified if the amplitude of a measure of flow or volume (detected by the thermocouple or thorax or abdominal inductance band signals) was reduced discernibly (at least 30% lower than baseline breathing) for at least 10 seconds and did not meet the criteria for apnea, and if the event was either associated with a 3% oxygen desaturation from baseline or terminated with electroencephalographic evidence of an arousal. For 4% only, hypopneas were identified if the aforementioned reduction in flow or volume occurred and the event was associated with a 4% oxygen desaturation from baseline. In both cases, an apnea was defined as a complete or almost complete cessation of airflow, as measured by the amplitude of the thermocouple signal, lasting at least 10 seconds.

Statistical analyses

Mean and standard deviation were used to provide an overall description of the data used in the analyses. For both definitions of the AHI, each participant's AHI was assigned to one of 4 OSA severity categories: no OSA (AHI < 5 events/h), mild (AHI ≥ 5 and < 15 events/h), moderate (AHI ≥15 and < 30 events/h), and severe (AHI ≥ 30 events/h). An analysis of variance or Student's *t* test was used to test for differences within continuous variables. Multiple linear regression was used to assess continuous relationships between AHI and BP. Inasmuch as the distribution of AHI was heavily skewed leftward and some values were 0, AHI was transformed using the natural log + 0.1 in the aforementioned analyses. Logistic regression and χ^2 were employed for categorical variables.

Three definitions of hypertension were used in these analyses. For each definition, the threshold BP for classifying a participant as hypertensive was used per the new American College of Cardiology/American Heart Association guidelines.[15] If participants met or exceeded the minimum threshold, then they were classified as positive for that definition. In addition, those who were taking antihypertensive medications but not meeting any of the BP definitions were classified as hypertensive. Thus, the definitions utilized were the following:

- Elevated or higher BP: BP > 120 mm Hg systolic and < 80 mm Hg diastolic
- Stage 1 or 2 hypertension: BP > 130 mm Hg systolic or > 80 mm Hg diastolic
- Stage 2 hypertension: BP > 140 mm Hg systolic or > 90 mm Hg diastolic
- Normotensive on antihypertensive medications

Hypertensive classification was based on the exam 2 BP unless values were missing (n = 175). In those cases, the BP at the FU exam was used.

Analyses were performed using IBM SPSS Statistics v.25 (Armonk, NY). $P < .05$ was considered statistically significant.

RESULTS

Of the 4,586 consenting exam 2 participants, there were 1,219 who were normotensive (BP < 120/80 mm Hg) and were not using antihypertensive medications at exam 1. Of this subset, 734 remained normotensive at exam 2. Of the remaining participants, 485 progressed to having an elevated BP (n = 208), stage 1 hypertension (n = 206), or stage 2 hypertension (n = 71), respectively. In addition, 68 of the 734 participants who were normotensive were taking antihypertensive medications (**Figure 1**), leaving 666 as participants with true normotension (ie, those who were not taking antihypertensive medications). Thus, including the group taking these medications, 553 participants developed hypertension between exams 1 and 2, resulting in an approximate 5-year incidence rate of 45.4%, or 8.6% annually. The demographic and anthropometric characteristics of these 4 groups are shown in **Table 1.**

At exam 2, 476 of 1,219 participants (39.0%) were classified as having OSA (AHI ≥ 5 events/h) at exam 1 by the 3%A criterion but not by the 4% only criterion. Of these 476 participants, OSA severity was mild (n = 429, 90.1%) and moderate to severe (n = 47, 9.9%). Incident hypertension rates in these participants with CMS-negative OSA for the American College of Cardiology/American Heart Association–defined BP categories[15] were 15% (elevated BP, n = 71), 15% (stage 1, n = 71), and 6% (stage 2, n = 30). There were also a small number of participants who were normotensive (4%, n = 19) who used hypertensive medications (**Figure 2**). If these latter participants were included as hypertensive, then the overall incidence rate of hypertension would be 40% (191/476) in those with CMS-negative OSA.

Table 2 displays the demographic, anthropometric, and OSA severity characteristics of the 476 participants who were identified as having OSA using the 3%A criterion but not the 4% only criterion for hypopneas. When the 191 participants who developed hypertension or elevated BP were compared with those who remained normotensive, there were no differences in the proportions of white participants or smokers. However, those who developed hypertension were older than those who were normotensive at exam 1, and there was a higher proportion of men; they also had a higher BMI and a greater change in BMI from exam 1 to exam 2. In addition, these participants had a higher prevalence of cardiovascular disease and stroke at exam 1. Follow-up polysomnograms were obtained after a mean of 5.3 ± 0.5 years in 313 of these participants with CMS-negative OSA. Participants who developed an elevated BP or hypertension had a greater proportion of moderate or severe OSA as defined by the 3%A criterion. Although AHI using both the 3%A and the 4% only criteria was higher in those who developed hypertension at exam 1, there was no change in AHI from exam 1 to exam 2 using either definition. When the components of the AHI were deconstructed, indices reflecting hypopneas identified by only a 3% or a 4% desaturation and by a 3% desaturation or arousal but not by an arousal alone were higher in those who developed an elevated BP or hypertension.

In the 476 participants identified as having OSA only by the 3%A hypopnea definition, the crude odds ratio for incident hypertension or elevated BP as a function of an AHI ≥ 15 events/h based on the 3%A criterion was 1.98 (95% confidence interval [CI], 1.08–3.64; $P = .027$). After adjusting for age and BMI, this odds ratio decreased to 1.79 (95% CI, 0.94–3.40; $P = .077$). In regression analyses within these 476 participants, AHI based on the 3%A criterion was associated positively with systolic BP (β = 4.14; 95% CI, 0.84–7.4; $P = .014$), but this relationship was severely attenuated and not statistically significant after

Figure 1—Flowchart of incident hypertension.

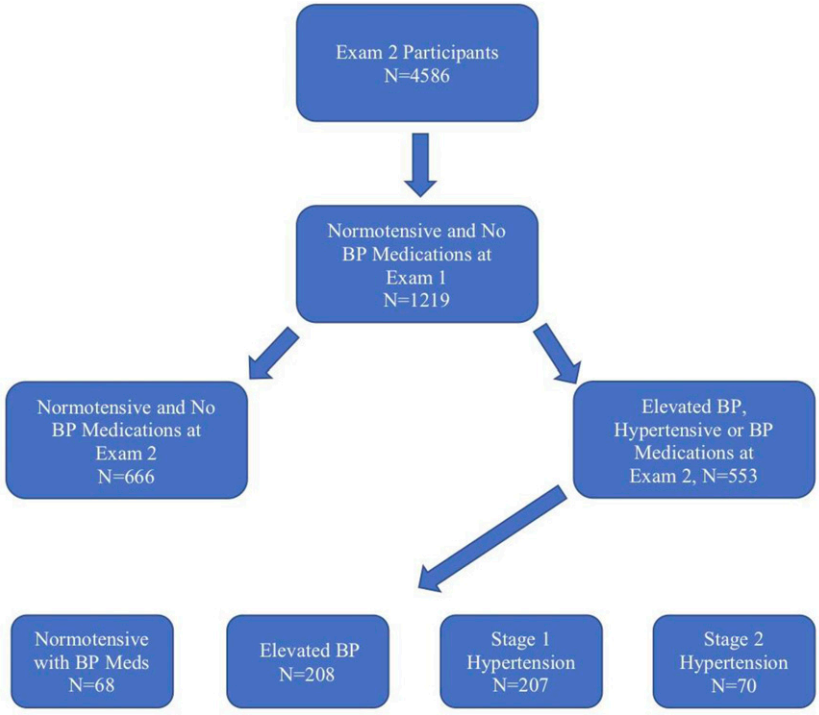


Table 1—Demographic and anthropometric characteristics of participants who were normotensive at exam 1, stratified by hypertension status at exam 2.

	Normal BP		BP Medications Only		Elevated BP		Stage 1 Hypertension		Stage 2 Hypertension		Total		*P* Value
	n	% or Mean ± SD	n	% or Mean ± SD	n	% or Mean ± SD	n	% or Mean ± SD	n	% or Mean ± SD	n	% or Mean ± SD	
% Men	666	35.7	68	50.0	208	41.3	207	43.0	70	42.9	1,219	39.1	.068
% White	666	84.7	68	82.4	208	82.7	207	78.2	70	74.4	1,219	82.5	.089
% Ever smoker	661	51.1	68	64.7	207	56.0	207	59.9	69	56.5	1,212	54.5	.071
Age exam 1	666	56.2 ± 10.0	68	60.5 ± 9.1	208	60.2 ± 9.4	207	59.3 ± 9.9	71	62.2 ± 11.0	1,219	58.0 ± 10.1	<.001
Age change from exam 1	598	5.3 ± 0.5	69	5.4 ± 0.5	208	5.3 ± 0.5	206	5.3 ± 0.5	71	5.4 ± 0.6	1,085	5.3 ± 0.5	.568
BMI exam 1 (kg/m^2)	664	26.2 ± 4.4	68	30.0 ± 5.9	208	27.6 ± 4.5	207	28.0 ± 4.3	70	26.9 ± 5.1	1,217	27.0 ± 4.6	<.001
BMI change from exam 1 (kg/m^2)	631	0.6 ± 2.3	66	0.6 ± 2.6	180	1.0 ± 2.0	155	1.0 ± 2.2	55	0.7 ± 2.4	1,021	0.8 ± 2.2	.128

BMI = body mass index, BP = blood pressure; SD = standard deviation.

adjustment for age, BMI, change in age, and change in BMI (β = 1.66; 95% CI, –1.85 to 5.17; *P* = .352). In contrast, AHI based on 3%A was associated with diastolic BP in bivariate analysis (β = 2.65; 95% CI, 0.48–4.81; *P* = .017) and remained statistically significant after adjustment for age, BMI, change in age, and change in BMI (β = 3.387; 95% CI, 1.08–5.69; *P* = .004).

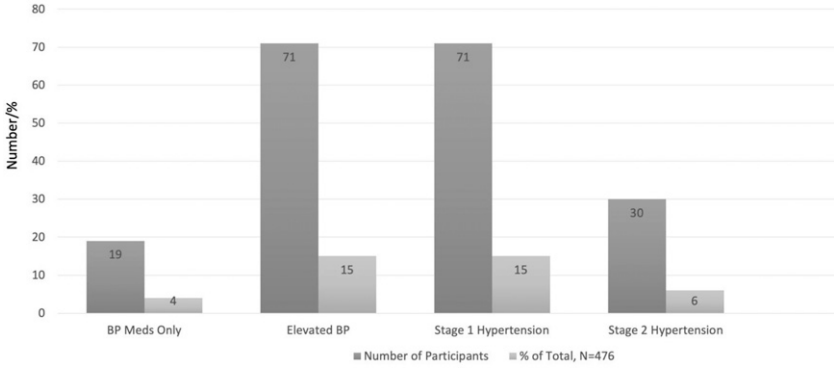
DISCUSSION

The data from this large prospective community-based study show that CMS-negative OSA is associated with incident hypertension. A significant proportion of participants in this group (40%) developed hypertension over a 5-year follow-up period.

Although cardiovascular morbidities, BMI, and age were higher in this group, our findings nevertheless add to the evidence indicating that use of the more stringent 4% only criterion for hypopnea as a component of the definition for OSA may exclude numerous patients who are at high risk of developing hypertension.

Our study is the first to calculate incidence rates of hypertension using the newly updated American College of Cardiology and American Heart Association definitions of

Figure 2—Incident hypertension in CMS-negative OSA.



CMS = Centers for Medicare & Medicaid Services.

hypertension.[15] Although our estimated annualized incidence rate of 8.6% seems higher than those reported from some studies and similar to others,[23] comparisons are not possible because previous surveys generally defined hypertension using older guidelines for blood pressure: > 140 mm Hg systolic or > 90 mm Hg diastolic.

Several studies have shown an association between OSA and various cardiovascular disorders.[24] OSA seems to have a causal relationship with hypertension.[8] Wisconsin Sleep Cohort Study data showed that an increasing severity of OSA was associated with an increase in the prevalence and incidence of hypertension.[25,26] Three large meta-analyses provided evidence of a significant decrease in BP with OSA therapy, further cementing the relationship between OSA and hypertension.[11–13] The benefit has been seen not only from OSA therapy with CPAP but also with mandibular advancement[13] and with surgical therapies.[27] Patients with refractory hypertension have shown an even greater improvement in BP than those with nonrefractory hypertension.[12] The results of the current study further support the association between OSA and hypertension and suggest that hypopneas associated with milder desaturation or arousal may also impact BP elevation.

Most studies assessing the association between OSA and hypertension have used a minimum 4% desaturation to define hypopneas.[20,25,28] Studies assessing the impact of hypopneas associated with less-pronounced desaturation have been scant. An initial analysis in the HypnoLaus study[29] showed that the 3%A hypopnea definition was associated cross-sectionally with hypertension, but a comparison to the 4% only definition was not performed. A subsequent analysis in the same cohort found that severe OSA identified with the 3%A hypopnea definition but not the 4% only definition was associated with a higher likelihood of hypertension.[30] Our earlier cross-sectional analyses from the Sleep Heart Health Study data also showed strong associations between OSA defined using the 3%A hypopnea criterion and hypertension.[16] That study suggested that using the more rigorous 4% only desaturation definition for hypopneas may lead to the misclassification of many patients with OSA as not having the condition.

Our current analyses extend these aforementioned studies by showing that a sizable cohort of individuals with OSA identified using the 3%A hypopnea criterion but not the 4% only criterion will develop an elevated BP or hypertension over an approximately 5-year interval. Although in our group of participants with CMS-negative OSA the elevated odds ratio for hypertension attributed to a higher AHI was attenuated by older age and a larger BMI, the finding that AHI based on the 3%A criterion predicted diastolic BP in a regression analysis supports a causal relationship. In the United States, CMS currently requires the use of the 4% only hypopnea definition to identify people with OSA and qualify them for therapy. Our data indicate that many patients with OSA may be precluded from receiving therapy and be at greater risk of developing hypertension.

Additional evidence supporting the importance of using the 3%A criterion to identify individuals with OSA can be found in 2 other recent analyses. In the DREAM cohort of veterans with a high proportion of hypertension,[31] the prevalence of CMS-negative OSA was 37.4%, which is comparable to the 39.0% observed in our study. Notably, those who had moderate to severe OSA in this group had a higher odds ratio for arrhythmias and ischemic heart disease, although the latter was attenuated and not quite statistically significant in a fully adjusted model. In the HypnoLaus study, significant associations were found between OSA defined by the 3%A criterion and diabetes and the metabolic syndrome.[30]

Several mechanisms have been proposed whereby OSA may enhance the risk of hypertension. Intermittent hypoxemia is only 1 of these pathophysiological factors. Although there is considerable evidence supporting its role in the pathogenesis of hypertension related to OSA, other factors may be important as well. These include sympathetic nervous activation from microarousals, intrathoracic pressure changes with apneic events, and inflammation from the repetitive upper airway collapse. Intermittent hypoxemia-reoxygenation can impair the vascular endothelium, leading to an imbalance between vasoconstrictors and vasodilators, abnormal cell proliferation, and hypercoagulability.[32] The role of microarousals in the causation of hypertension has been debated. Our results did not find that hypopneas identified by arousals alone predicted the development of hypertension. However, our sample size may have been too small to detect an effect given that arousal scoring can be less precise than identification of apneas or

Table 2—Comparison of demographic, anthropometric, and OSA severity characteristics of participants who were nonhypertensive and incident hypertensive with OSA as defined by AASM standards but not by CMS standards at exam 1.

	No Hypertension n = 285		Elevated BP, Stage 1 or 2 Hypertension n = 191		Total n = 476		*P* Value
	n	% or Mean ± SD	n	% or Mean ± SD	n	% or Mean ± SD	
Sex							
% Men	103	36.1	86	45.0	189	39.7	.056
% Women	182	63.9	105	55.0	287	60.3	
Race							
% White	240	84.2	158	82.7	398	83.6	.667
% Other	45	15.8	13	17.3	78	16.4	
Smoking							
% Ever	139	49.3	105	55.6	244	51.8	.182
% Never	143	50.7	84	44.4	471	48.2	
CVD: % prevalence	3	1.1	12	6.3	15	3.2	.002
Stroke: % prevalence	1	0.4	4	2.1	5	1.1	.086
OSA severity: % moderate/severe	21	7.4	26	13.6	47	9.9	.029
Age exam 1 (y)	285	55.9 ± 9.4	191	60.2 ± 9.6	476	57.6 ± 9.7	<.001
BMI exam 1 (kg/m^2)	281	25.4 ± 3.8	190	26.6 ± 3.8	471	25.9 ± 3.9	.001
Change in BMI exam 2-exam 1 (kg/m^2)	285	0.6 ± 2.2	191	1.1 ± 2.1	476	0.8 ± 2.1	.009
Systolic BP	285	109 ± 8	191	129 ± 12	476	117 ± 13	<.001
Diastolic BP	285	67 ± 7	190	73 ± 10	475	69 ± 9	<.001
AHI (3%A)[a]	285	9.1 ± 3.4	191	10.5 ± 4.6	476	9.7 ± 4.0	<.001
Apnea index	285	1.1 ± 1.6	191	1.2 ± 2.1	476	1.1 ± 1.9	.770
HI 3%Arousal[b]	285	8.3 ± 3.2	191	9.6 ± 4.1	476	8.8 ± 3.7	<.001
HI 3%[c]	285	4.5 ± 2.4	191	5.6 ± 3.0	476	4.9 ± 2.7	<.001
HI-Arousal[d]	285	3.8 ± 2.4	191	4.0 ± 2.7	476	3.9 ± 2.5	.345
Change in AHI exam 2-exam 1 (3%A)[e,f]	192	2.9 ± 10.7	119	1.4 ± 8.4	311	2.4 ± 9.9	.203
AHI (4%)[g]	285	2.0 ± 1.2	191	2.5 ± 1.3	476	2.2 ± 1.3	<.001
HI 4%[h]	285	1.6 ± 1.1	191	2.1 ± 1.3	476	1.8 ± 1.2	<.001
Change in AHI exam 2-exam 1 (4% only)[f,i]	193	3.7 ± 7.9	120	2.8 ± 5.0	313	3.3 ± 6.0	.259

[a]AHI at exam 1 defined using 3%A hypopnea definition.
[b]HI defined by ≥ 3% oxygen desaturation or arousal.
[c]HI defined by only a ≥ 3% oxygen desaturation.
[d]HI defined only by the presence of an arousal.
[e]AHI at exams 1 and 2 defined using 3%A hypopnea definition.
[f]Polysomnography not performed at exam 2 in some participants.
[g]AHI at exam 1 defined using 4% only hypopnea definition.
[h]HI defined only by a ≥ 4% oxygen desaturation.
[i]AHI at exams 1 and 2 defined using 4% only hypopnea definition.
AASM = American Academy of Sleep Medicine, BMI = body mass index, BP = blood pressure, CMS = Centers for Medicare & Medicaid Services, CVD = cardiovascular disease (ie, myocardial infarction, coronary artery bypass/angioplasty, heart failure), HI = hypopnea index, SD = standard deviation.

hypopneas. Nevertheless, small studies and data from the larger Cleveland Family Study have shown an association between arousals and an increase in BP or hypertension.[33–35] In addition, even if arousals do not play a major role in the pathogenesis of hypertension related to OSA, then they do seem to be important in identifying individuals with OSA without hypoxemia who experience daytime sleepiness.[36,37]

Our study does have some limitations. Whereas the current study supports the relationship between CMS-negative OSA and hypertension, the sample size was relatively small, which could be a factor resulting in a borderline type 1 error of 0.077 between a diagnosis of moderate to severe OSA and the development of hypertension or elevated BP. The use of voluminous databases, or "big data," in future studies may provide more compelling evidence regarding this association.[38] Sleepiness is present in almost half of people with OSA[39] and may potentially mediate the association between OSA and hypertension. It is possible that the relationship between OSA and hypertension in this study may have been more robust if we had selected only those with self-reported sleepiness, but this would have severely constrained our sample size. The participants included in our analyses had predominantly mild OSA. Not infrequently, there are

patients with severe CMS-negative OSA. The impact of more frequent nightly arousals during sleep in such patients cannot be determined from our data, and further studies are necessary. Finally, our study does not address the potential impact of CMS-negative OSA on mortality and on cardiovascular outcomes such as coronary heart disease and stroke.

The strengths of the current study include a well-characterized population and a long follow-up period of > 5 years. The participants were recruited from community groups, thus limiting the referral bias; all participants underwent polysomnograms, currently considered the gold standard in the diagnosis of sleep apnea; and blood pressure measurements were performed using a standard protocol. Finally, we analyzed the impact of CMS-negative OSA using the most recent definitions of hypertension from the American College of Cardiology and the American Heart Association.

CONCLUSIONS

In summary, this study provides evidence that OSA defined by milder desaturation and arousals may be a risk for incident hypertension. It suggests that current CMS guidelines, by denying reimbursement for OSA treatment, place some individuals with OSA at greater risk of developing hypertension.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
BMI, body mass index
BP, blood pressure
CI, confidence interval
CMS, Centers for Medicare & Medicaid Services
CMS-negative OSA, Centers for Medicare & Medicaid Services–negative OSA
4% only, 4% oxygen desaturation criterion
SD, standard deviation
3%A, 3% oxygen desaturation or arousal criterion

REFERENCES

1. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2012;8(5):597–619.
2. Ciftci TU, Kokturk O, Ozkan S. Apnea-hypopnea indexes calculated using different hypopnea definitions and their relation to major symptoms. *Sleep Breath.* 2004;8(3):141–146.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993; 328(17):1230–1235.
4. Gottlieb DJ, Yenokyan G, Newman AB, et al. A prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. *Circulation*. 2010;122(4):352–360.
5. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046–1053.
6. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177(9): 1006–1014.
7. Shamim-Uzzaman QA, Singh S, Chowdhuri S. Hypopnea definitions, determinants and dilemmas: a focused review. *Sleep Sci Pract.* 2018;2(1):7.
8. Budhiraja R, Sharief I, Quan SF. Sleep disordered breathing and hypertension. *J Clin Sleep Med.* 2005;1(4):401–404.
9. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307(20): 2169–2176.
10. Budhiraja R, Budhiraja P, Quan SF. Sleep-disordered breathing and cardiovascular disorders. *Respir Care*. 2010;55(10):1322–1332.
11. Fava C, Dorigoni S, Dalle Vedove F, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea: a systematic review and meta-analysis. *Chest*. 2014; 145(4):762–771.
12. Iftikhar IH, Valentine CW, Bittencourt LR, et al. Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis. *J Hypertens.* 2014;32(12):2341–2350; discussion 2350.
13. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA*. 2015;314(21):2280–2293.
14. Budhiraja R, Quan SF. When is CPAP an antihypertensive in sleep apnea patients? *J Clin Sleep Med.* 2009;5(2):108–109.
15. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):1269–1324.
16. Budhiraja R, Javaheri S, Parthasarathy S, Berry RB, Quan SF. The association between obstructive sleep apnea characterized by a minimum 3 percent oxygen desaturation or arousal hypopnea definition and hypertension. *J Clin Sleep Med.* 2019;15(9):1261–1270.
17. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20(12):1077–1085.
18. Lind BK, Goodwin JL, Hill JG, Ali T, Redline S, Quan SF. Recruitment of healthy adults into a study of overnight sleep monitoring in the home: experience of the Sleep Heart Health Study. *Sleep Breath.* 2003;7(1):13–24.
19. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study.Sleep Heart Health Research Group. *Sleep*. 1998;21(7):759–767.
20. O'Connor GT, Caffo B, Newman AB, et al. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2009;179(12):1159–1164.
21. Whitney CW, Gottlieb DJ, Redline S, et al. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep*. 1998;21(7):749–757.
22. Rechtschaffen A, Kales A, eds. *A Manual for Standardized Terminology, Techniques and Scoring System for Sleep Stages in Human Subjects.* University of California, Los Angeles: U.S. National Institute of Neurological Diseases and Blindness, Neurological Information Network; 1968.
23. Hajjar I, Kotchen JM, Kotchen TA. Hypertension: trends in prevalence, incidence, and control. *Annu Rev Public Health*. 2006;27(1):465–490.
24. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol.* 2017; 69(7):841–858.
25. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* 2000; 342(19):1378–1384.
26. Peppard PE. Is obstructive sleep apnea a risk factor for hypertension?—differences between the Wisconsin Sleep Cohort and the Sleep Heart Health Study. *J Clin Sleep Med.* 2009;5(5):404–405.
27. Halle TR, Oh MS, Collop NA, Quyyumi AA, Bliwise DL, Dedhia RC. Surgical treatment of OSA on cardiovascular outcomes: a systematic review. *Chest*. 2017; 152(6):1214–1229.

28. Mansukhani MP, Kolla BP, Wang Z, Morgenthaler TI. Effect of varying definitions of hypopnea on the diagnosis and clinical outcomes of sleep-disordered breathing: a systematic review and meta-analysis. *J Clin Sleep Med.* 2019;15(5):687–696.
29. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med.* 2015;3(4):310–318.
30. Hirotsu C, Haba-Rubio J, Andries D, et al. Effect of three hypopnea scoring criteria on OSA prevalence and associated comorbidities in the general population. *J Clin Sleep Med.* 2019;15(2):183–194.
31. Won CHJ, Qin L, Selim B, Yaggi HK. Varying hypopnea definitions affect obstructive sleep apnea severity classification and association with cardiovascular disease. *J Clin Sleep Med.* 2018;14(12):1987–1994.
32. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. *J Clin Sleep Med.* 2007;3(4):409–415.
33. Yoon IY, Jeong DU. Degree of arousal is most correlated with blood pressure reactivity during sleep in obstructive sleep apnea. *J Korean Med Sci.* 2001;16(6): 707–711.
34. Nisbet LC, Yiallourou SR, Nixon GM, et al. Characterization of the acute pulse transit time response to obstructive apneas and hypopneas in preschool children with sleep-disordered breathing. *Sleep Med.* 2013;14(11):1123–1131.
35. Sulit L, Storfer-Isser A, Kirchner HL, Redline S. Differences in polysomnography predictors for hypertension and impaired glucose tolerance. *Sleep*. 2006;29(6): 777–783.
36. Guilleminault C, Hagen CC, Huynh NT. Comparison of hypopnea definitions in lean patients with known obstructive sleep apnea hypopnea syndrome (OSAHS). *Sleep Breath.* 2009;13(4):341–347.
37. Koch H, Schneider LD, Finn LA, et al. Breathing disturbances without hypoxia are associated with objective sleepiness in sleep apnea. *Sleep*. 2017;40(11): zsx152.
38. Budhiraja R, Thomas R, Kim M, Redline S. The role of big data in the management of sleep-disordered breathing. *Sleep Med Clin.* 2016;11(2):241–255.
39. Budhiraja R, Kushida CA, Nichols DA, et al. Predictors of sleepiness in obstructive sleep apnoea at baseline and after 6 months of continuous positive airway pressure therapy. *Eur Respir J.* 2017;50(5):1700348.

ACKNOWLEDGMENTS

The Sleep Heart Health Study was supported by National Heart, Lung, and Blood Institute cooperative agreements U01HL53940 (University of Washington), U01HL53941 (Boston University), U01HL53938 (University of Arizona), U01HL53916 (University of California, Davis), U01HL53934 (University of Minnesota), U01HL53931 (New York University), U01HL53937 and U01HL64360 (Johns Hopkins University), U01HL63463 (Case Western Reserve University), and U01HL63429 (Missouri Breaks Research). A list of SHHS investigators, staff, and participating institutions is available on the SHHS website, http://jhuccs1.us/shhs/details/investigators.htm.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May 12, 2020
Submitted in final revised form July 1, 2020
Accepted for publication July 1, 2020
Address correspondence to: Stuart F. Quan, MD, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115; Tel: (617) 983-7489; Fax: (617) 983-2488; Email: Stuart_Quan@hms.harvard.edu

DISCLOSURE STATEMENT

All authors have read and approved this manuscript. Work for this study was performed at Brigham and Women's Hospital and the University of Arizona College of Medicine. Dr. Budhiraja reports no conflicts of interest or grant funding. Dr. Javaheri serves as a consultant for Jazz Pharmaceuticals and Harmony Biosciences. Dr. Parthasarathy reports grants from the National Institutes of Health/National Heart, Lung and Blood Institute as the principal investigator (HL138377, HL126140; IPA-014264-00001; HL095799) or site PI (HL128954; UG3HL140144); other National Institutes of Health grants (AG059202, OD028307, HL151254); grants from the Patient Centered Outcomes Research Institute as the PI (IHS-1306-02505; EAIN-3394-UOA) or site investigator (PCS-1504-30430) and other grants (DI-2018C2-13161, PPRND-1507-31666) during the writing of the manuscript; grants from the U.S. Department of Defense as coinvestigator (W81XWH-14-1-0570); grants from the National Institutes of Health/ National Cancer Institute as coinvestigator (R21CA184920) and the National Institutes of Health/National Institute on Minority Health and Health Disparities as coinvestigator (MD011600); grants from the Johrei Institute; personal fees from the American Academy of Sleep Medicine; nonfinancial support from the National Center for Sleep Disorders Research of the National Institutes of Health (National Heart, Lung, and Blood Institute); personal fees from UpToDate Inc.; grants from Younes Sleep Technologies, Ltd.; personal fees from Vapotherm, Inc.; personal fees from Merck, Inc.; grants and personal fees from Philips-Respironics, Inc.; personal fees from Bayer, Inc.; personal fees from Nightbalance, Inc.; personal fees from Merck, Inc.; and grants from the American Academy of Sleep Medicine Foundation (169-SR-17). In addition, Dr. Parthasarathy has a patent issued (UA 14-018 U.S.S.N. 61/884,654; PTAS 502570970; home breathing device). Dr. Berry reports research funding from Philips Respironics, Res Med, and the University of Florida Foundation. Dr. Quan reports research funding from the National Institutes of Health, serves as a consultant to Jazz Pharmaceuticals and Whispersom, and is a committee chair and hypopnea task force member for the American Academy of Sleep Medicine.