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Resistant Hypertension and Obstructive Sleep Apnea in the Setting of Kidney Disease

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Abstract

Objectives—To explore the relationship between obstructive sleep apnea (OSA) and resistant hypertension in chronic kidney disease (CKD) and end-stage renal disease (ESRD).

Methods—We examined sleep parameters and blood pressure (BP) in 224 community-based, non-CKD participants from the Sleep-SCORE study, 88 non-dialysis dependent CKD and 95 ESRD participants. Unattended home polysomnography with standardized scoring protocols and automated BP monitors were used. Resistant hypertension was defined as a BP ≥140/90 mmHg despite ≥3 antihypertensives.

Results—Mean systolic BP of the CKD and ESRD groups were significantly higher than the non-CKD group (148.2mmHg [23.8], 144.5mmHg [26.7] vs. 132.2mmHg [26.7], respectively; $P<0.0001$) despite the use of more anti-hypertensive medications. The CKD and ESRD groups had higher rates of resistant hypertension than the non-CKD group (41.4%, 22.6% vs. 6.7%, respectively; $P<0.0001$). The severity of sleep apnea was associated with a higher risk of resistant hypertension. While resistant hypertension was associated with severe sleep apnea in participants with ESRD (odds ratio [OR] 7.1, 95% confidence interval [CI] 2.2-23.2), there was no significant association in the non-CKD (OR 3.5, 95% CI 0.8-15.4) or CKD groups (OR 1.2, 95% CI 0.4-3.7) after accounting for case-mix.

Conclusion—The association between resistant hypertension and sleep apnea appeared robust in ESRD. OSA may contribute to resistant hypertension or both may be linked to a common underlying process such as volume excess. Future studies in patients with kidney disease should further characterize the resistant hypertension - OSA relationship and determine whether treatment of underlying mechanisms may improve outcomes.

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Conflicts of Interest

No conflicts were declared.

Keywords

Sleep apnea; chronic kidney disease; end-stage renal disease; hypertension; resistant hypertension

Introduction

Hypertension (HTN) is one of the most common diagnoses for outpatient medical visits [1]. Approximately, 15 to 20% of hypertensive patients have resistant hypertension (RH) [2]. RH, defined as the failure to achieve a target blood pressure (BP) of <140/90 despite the use of 3 or more antihypertensive drugs (including a diuretic) at adequate doses, has been associated with poor outcomes including an increased risk of end-organ damage and cardiovascular events [3].

Specific factors, such as older age, obesity, and African-American race have been independently associated with higher rates of uncontrolled hypertension in both the general population and among those with kidney disease [4]; however, the contribution of sleep disorders to RH remains incompletely characterized. Obstructive sleep apnea (OSA) is common in patients with HTN, with a prevalence of up to 50% [5]. Previous literature suggests that OSA may be an independent risk factor for RH in the general population [2, 6]. Unfortunately, studies examining the link between OSA and RH have explicitly excluded patients with moderate to severe chronic kidney disease (CKD) or have had relatively few patients with advanced CKD [6-10].

OSA in the setting of advanced kidney disease may differ from that in the general population. For example, obesity, witnessed apneas, and unrefreshing sleep are not as prevalent in end-stage renal disease (ESRD) patients with OSA compared to their general population counterparts [11]. In addition, hemodialysis (HD) patients exhibit a markedly increased risk of OSA and severe nocturnal hypoxemia even after adjusting for age, sex, race, and body mass index (BMI) [12]. Further, OSA may have important detrimental effects in kidney disease patients, potentially hastening progression of CKD [13] and increasing mortality in ESRD [11]. Given these differences, it may not be accurate to extrapolate the independent association between RH and OSA in patients with normal renal function to patients with CKD or ESRD.

In this study we examined the association of OSA with RH in ESRD, non-dialysis dependent CKD, and community based non-CKD participants taken from a representative population sample, the Pittsburgh SleepSCORE Project [14, 15]. We also explore whether other sleep parameters such as sleep time and periodic limb movements are associated with RH.

Materials and Methods

Study Setting, Design, Participants

As part of a previously described [16, 17] larger prospective cohort study investigating memory, sleep, and quality of life in adult, English-speaking patients with advanced chronic kidney disease (dialysis dependence or Modification of Diet in Renal Disease [MDRD] estimated glomerular filtration rate [eGFR] <40 ml/min/1.73m²), we approached patients during their routine CKD clinic visit, dialysis clinic visit, or their initial evaluation at a kidney transplantation clinic between March 2004 and December 2008. Exclusion criteria included age <18 years or >90 years, use of continuous positive airway pressure (CPAP), and active psychiatric or medical disease (e.g. unstable angina) [16, 17]. As of December 2008, 183 CKD/ESRD patients provided written informed consent and completed home

polysomnography (PSG) assessments. Seventy-five were on HD, 20 on peritoneal dialysis (PD), and 88 had non-dialysis dependent CKD.

For this report, 224 non-CKD participants were taken from the Sleep-SCORE study, a single-center, prospective community-based cohort study investigating the relationship between sleep/awake BP and sleep disturbances [14, 15]. Baseline enrollment began on June 16, 2003 and ended on October 11, 2006. The Sleep-SCORE study recruited participants with high/moderate or low Framingham risk scores and enrolled nearly equal ratios of men/women and African-American/Caucasian participants. Eligibility criteria included age between 45 and 75 years, residence in the greater Pittsburgh metropolitan area, and absence of comorbid conditions expected to limit life expectancy to <5 years. Exclusion criteria included pregnancy, use of CPAP for sleep-disordered breathing, regular use of sleep medications, night shift work schedule, medications for diabetes, a prior diagnosis of stroke or myocardial infarction, or a history of interventional cardiology procedures.

These studies were observational in nature; all participants received hypertension treatment managed by their regular physicians. All participants provided written informed consent and the University of Pittsburgh Institutional Review Board approved each study.

Data Collection

For all participants, the baseline data collection included a brief standardized health interview and questionnaire; assessment of current antihypertensive medication use; measurement of height, weight, and neck circumference. Age, sex, race, education, employment, and smoking status were self-reported. A history of physician-diagnosed medical illnesses, previous surgical treatments, or medical procedures was obtained during the health interview. Additionally, for the CKD and ESRD participants, standard serum laboratory tests drawn 3 months prior to or following the PSG completion date were abstracted from the medical record. Non-CKD (i.e., Sleep-SCORE) participants had a fasting venous blood draw for metabolic, inflammatory, and standard laboratory measures.

Self-Reported Sleep Assessment

Participants completed the Epworth Sleepiness Scale (ESS) [18], an 8-item subjective measure of self-reported sleep tendency. Scores 10 generally reflect excessive daytime sleepiness. Participants also completed the Pittsburgh Sleep Quality Index (PSQI) [19], a self-report questionnaire that assesses sleep quality over the previous month. Higher PSQI scores reflect poorer sleep quality.

PSG Sleep Assessment

One unattended in-home PSG was performed using an ambulatory Compumedics Siesta monitor (Charlotte, North Carolina) at habitual sleep times in all participants. For HD patients, patient preference determined when nocturnal polysomnography (PSG) was conducted relative to the day of HD. For the 72 of 75 HD patients with available data, 34 (45%) were studied the evening of their HD session and 38 (51%) were studied the evening before their HD session.

The PSG montage was the same for all participants and included bilateral central and occipital electro-encephalogram channels, bilateral electro-oculogram, and bipolar submental is electromyogram. Bipolar electrocardiogram and position sensors were used to monitor heart rate and body position, respectively. Participants were also monitored for respiratory parameters, nasal pressure and for abdominal and thoracic effort using finger pulse oximetry (Nonin, Minneapolis, MN), nasal-oral thermocouple, and inductance

plethysmography, respectively. In addition, Sleep-SCORE participants were studied using two nights of PSG [14, 15]. This report uses only the first night's sleep study.

Sleep study data processing and scoring followed identical procedures in all participants [14, 15]. Centrally trained PSG technologists scored sleep records according to the Rechtschaffen and Kales guidelines using standard sleep stage scoring criteria for each 20-s epoch [20]. The same technologists were involved in scoring all study groups. All scorers were blinded to the status of the patients' renal function. Standard definitions were used to identify apneas and hypopneas [21]; oximetry readings were used to quantify average and minimum oxygen saturation levels.

PSG outcome variables in the analysis included total sleep time (TST, minutes of any stage sleep between sleep onset and final awakening), sleep architecture (percentage of TST spent in Stage 1, Stage 2, Stages 3-4, and rapid eye movement [REM] sleep), and the apnea-hypopnea index (AHI, number of apneas/hypopneas per hour of sleep) [22]. Severe OSA was defined as an AHI ≥ 30 .

Blood Pressure

For all participants, two measurements of systolic BP (SBP) and diastolic BP (DBP) were performed in the participant's home on the evening of the sleep study (prior to sleep study initiation). For patients with CKD or ESRD, an Omron cuff was used for both measures and the mean of the two measures was used. For the non-CKD participants, one of the measurements used an Omron cuff and one was obtained by a trained research technician using a mercury cuff. If there was a >4 -6 mmHg discrepancy between the Omron and mercury measures, a third measurement was performed using the mercury cuff. The mean of the two values (either Omron and mercury if no discrepancy existed or two mercury cuff readings if a discrepancy was noted) was used. RH was defined as BP $> 140/90$ mmHg in the setting of at least three BP-lowering drugs.

Statistical Analysis

Baseline demographics, laboratory values and sleep measures were described using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences between groups were assessed using analysis of variance or the Kruskal Wallis test for continuous variables and a chi-square test for categorical variables. When differences in continuous variables were noted, pairwise comparisons were performed using t-tests or Wilcoxon-Mann-Whitney tests.

Logistic regression was used to examine crude and adjusted associations of severe OSA with RH in each of the patient subgroups. Based on prior literature [4, 23], the multivariate model adjusted for known confounders such as age, sex, race, and BMI. A case-mix adjusted logistic regression model was also used to examine independent associations with RH in the total participant sample. The case-mix model adjusted for age, sex, race, BMI, and non-CKD/CKD/ESRD status. The strength of association for age, sex, race, and BMI were also examined in the baseline case-mix adjusted model. For all analyses, P values < 0.05 were considered significant. Analyses were performed using SAS (version 8.1; SAS Institute, Cary, NC).

Results

Participant Characteristics

Baseline characteristics of our sample are shown in Table 1. The CKD and ESRD groups were younger than the non-CKD group. The non-CKD and ESRD groups had significantly

fewer men and a higher proportion of African-Americans than the CKD group. The ESRD group had a lower BMI than the non-CKD group. Serum creatinine and eGFR significantly differed between groups as expected. The non-CKD and CKD groups had higher TST and sleep efficiency than the ESRD group. The ESRD group had a higher mean AHI than the non-CKD group. Both the CKD and the ESRD groups had a higher proportion of participants suffering from severe OSA (AHI ≥ 30) than the non-CKD group. The non-CKD and CKD groups also reported lower PSQI scores compared to the ESRD group. AHI did not differ for HD participants studied on HD evenings versus those studied on non-HD evenings (data not shown).

Blood Pressure

Both the CKD and ESRD groups had significantly higher SBP compared to the non-CKD group (Table 2); the study groups did not differ in DBP. The non-CKD group was prescribed the fewest number of anti-hypertensives followed by the ESRD group and then the CKD group. When a goal BP of 130/80 mmHg was used, RH was most frequent among CKD patients, then ESRD patients, and least frequent among non-CKD patients (Table 2). Using a BP cutoff of 140/90 mmHg, ESRD and CKD participants were not significantly different; however, both exhibited higher rates of RH than non-CKD participants (Table 2).

Association of RH with Sleep Apnea

The unadjusted and adjusted (for age, sex, race, BMI) odds of RH in patients with severe OSA (AHI ≥ 30) in each subgroup is shown in Figure 1. In the non-CKD group, a trend towards an increased odds for RH was noted in both unadjusted and adjusted analyses; however, these did not reach statistical significance (adjusted odds ratio and 95% confidence interval [CI]: 3.5 [0.8-15.4]). In CKD participants, no association was apparent in either unadjusted or adjusted analyses (adjusted odds ratio and 95% CI: 1.2 [0.4-3.7]). Among ESRD participants, an association was noted in both unadjusted and adjusted analyses (adjusted odds ratio and 95% CI 7.1 [2.2-23.2]).

In sensitivity analyses, using an AHI ≥ 15 , a RH BP cut-off of $>130/80$, or excluding participants with atrial fibrillation did not qualitatively alter the findings. However, re-defining RH to require the use of a diuretic in non-ESRD patients resulted in the reclassification of 4 non-CKD participants and a subsequently significant association between RH and OSA in non-CKD participants. The odds of RH in the setting of severe sleep apnea in non-CKD participants increased to OR 6.8 (95% CI 1.4-32.4, $p=0.02$) in unadjusted analysis and OR 6.9 (95% CI 1.3-36.1, $p=0.02$) in age, sex, race, BMI adjusted analyses.

Crude and Case-Mix Adjusted Associations with RH

Variables noted to be associated with RH in the crude analysis of all participants were male gender, increased AHI/severe sleep apnea (AHI ≥ 30), and lower total sleep time (Table 3). In the case-mix adjusted model (adjusted for age, gender, race, BMI, and kidney disease status), only African-American race and AHI/severe sleep apnea (AHI ≥ 30) were independently associated with RH (Table 3). Other sleep parameters including periodic limb movement index and percentage of TST spent in REM were not associated with RH in either crude or adjusted analyses (data not shown for percentage of TST spent in Stage 1, Stage 2, Stages 3-4, and REM sleep).

Discussion

In this study, we observed that RH and severe OSA (AHI ≥ 30) were significantly more prevalent in patients with advanced kidney disease. Approximately 30% of kidney disease

participants had RH and nearly 25% had severe OSA. In addition, ESRD patients with severe OSA were seven-fold more likely to have RH than their counterparts. However, severe sleep apnea was not independently associated with RH in advanced non-dialysis dependent CKD. In the total participant sample, after adjusting for case-mix, AHI and severe OSA (AHI ≥ 30) were independently associated with RH.

Previous studies in the general population have demonstrated a correlation between OSA and RH [2, 6, 24, 25]. However, many of these studies either excluded patients with moderate to advanced CKD or did not report participant renal function and likely had a low prevalence of advanced CKD [2, 6, 9, 10, 24-26]. This report extends prior findings of an independent association between RH and OSA to the ESRD population. Recent findings implicate underlying volume excess and nocturnal rostral fluid shifts as potential links between RH and OSA in the general population [5, 7, 9, 26, 27]. Patients with ESRD are particularly susceptible to developing volume excess, and this may contribute to RH and OSA. Previous work demonstrated that more effective ultrafiltration during renal replacement therapy improved OSA [28, 29] and BP control [30-33] in ESRD patients. These findings reinforce the potential importance of optimal volume management in the setting of ESRD. Future studies are needed to determine whether nocturnal fluid shifts help explain the high rate of OSA in ESRD patients [12] and if strategies to improve volume status, BP, and OSA in ESRD can improve morbidity, mortality, and quality of life.

Other mechanisms, such as increased aldosterone levels may also link RH and OSA. For example, in animal models, OSA and its consequent hypoxia upregulate the sympathetic nervous system and the renin-angiotensin system [34-37]. Recent studies have also identified increased aldosterone levels in participants with RH and OSA [9, 26, 27]. In one study [38], the use of an aldosterone antagonist in participants with RH improved their OSA. Whether these effects are predominantly volume mediated or a complex combination of volume, vascular, and endothelial changes has not been fully elucidated.

We did not observe an independent association between RH and OSA in non-dialysis dependent CKD. However, participants with non-dialysis dependent CKD were prescribed a larger number of anti-hypertensives and were generally more likely to have RH. While volume excess and renin-angiotensin mediated mechanisms contribute to the difficulty to manage hypertension associated with non-dialysis dependent CKD, many additional factors play an important role [39]. These include sympathetic nervous system activation, renal ischemia, reduced nitric oxide and elevated endothelin production [39]. Differences in the pathophysiology of RH in non-dialysis dependent CKD could explain the lack of a significant association between RH and OSA in this setting. Larger studies are needed to corroborate our findings.

In contrast to a recent report comparing patients with controlled and uncontrolled RH [6], we did not note an independent association between RH and REM sleep. Prior animal data indicate that BP increases in response to REM sleep deprivation [40, 41] and this suggests that sleep architecture may play a role in RH. However, there is limited data in humans to support this hypothesis and further research is needed to determine whether REM sleep is associated with RH. Similarly, while previous studies have observed higher BPs in patients with decreased sleep time [42-44], in our sample TST was not independently associated with RH. This corroborates similar findings by Ruttanaumpawan and colleagues [6].

This study has a number of strengths. It examined a relatively large number of participants with kidney disease. CKD patients are at substantial risk for RH and OSA but have been largely excluded from prior OSA-RH studies. In addition, we used standardized PSG assessments and scoring across study groups. Further, we adjusted for important

confounding variables in examining the association of RH and OSA including age, sex, race, and BMI. However, our findings should be considered in light of several limitations. First, our study was cross-sectional and associations do not prove causality. Second, while we controlled for age, sex, race and BMI in many of our analyses, we cannot exclude confounding. Third, while comparable to previous studies [2, 6, 10], we had a relatively small sample of participants with RH. Fourth, we used unattended in-home PSG. However, prior studies using home PSG have duplicated findings from studies using full PSG performed in the sleep lab [2, 45]. Finally, we did not attempt to assess pathophysiologic mechanisms that may explain the RH-OSA association (e.g., volume status, renin-angiotensin-aldosterone levels).

In summary, patients with kidney disease have a high prevalence of RH and OSA. Patients with ESRD and severe OSA are more than seven times as likely to have RH. However, patients with non-dialysis dependent CKD and severe OSA did not appear to be at increased risk for RH. Further studies are needed to clarify the potential pathophysiologic links between RH and OSA in the setting of kidney disease.

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Figure 1.

Odds of resistant hypertension in the setting of severe sleep apnea

* Adjusted for age, sex, race, body mass index.

CI confidence interval, ESRD end-stage renal disease, CKD chronic kidney disease

Table 1

Baseline characteristics

	Non-CKD n =224	CKD n =88	ESRD n =95	P-Value [†]
Demographics				
Age	60.0 (7.2)	52.2 (14.1)	53.8 (14.9)	<0.0001 ^{a,b}
Male	113 (50.5)	60 (68.2)	56 (59.0)	0.02 ^{a,c}
African-American	97 (43.3)	19 (21.6)	38 (40.0)	0.002 ^{a,c}
Married	140 (62.5)	52 (59.1)	54 (56.8)	0.61
Student/employed	136 (60.7)	40 (45.5)	19 (20.0)	<0.0001 ^{a,b,c}
Education (12 th grade)	188 (83.9)	81 (92.1)	82 (86.3)	0.17
Clinical Characteristics				
Active smoker	19 (8.5)	12 (13.6)	12 (12.6)	0.31
Neck circumference (cm)	39.2 (4.1)	39.4 (8.2)	39.6 (6.1)	0.75 [*]
BMI (kg/m ²)	29.5 (5.0)	28.4 (5.3)	27.5 (5.5)	0.004 ^b
Creatinine (μmol/L)	84.6 (16.0)	399.7 (256.2)	772.5 (269.2)	<0.0001 ^{a,b,c}
eGFR (ml/min/1.73m ²)	91.8 (19.2)	18.9 (7.6)	---	<0.0001 ^a
PSG				
Total Sleep Time (hours)	6.1 (1.4)	6.0 (1.7)	5.3 (2.0)	< 0.001 ^{a,b,c}
Sleep efficiency	76.5 (13.1)	74.4 (14.8)	69.3 (16.1)	0.0003 ^{b,c}
% Stage 1	10.2 (6.8)	12.0 (9.2)	13.0 (10.5)	0.08 [*]
% Stage 2	62.9 (9.2)	61.0 (12.1)	57.4 (13.4)	0.0007 ^{a,b}
% Delta	5.0 (6.0)	7.6 (9.4)	11.2 (10.6)	0.0001 ^{a,b,c}
% REM	21.8 (6.5)	19.3 (8.3)	18.4 (9.2)	0.001 ^{a,b}
PLM Index (per hour)	5.4 (6.0)	3.6 (3.5)	4.9 (5.7)	0.005 ^a
AHI (per hour)	13.4 (15.0)	18.5 (22.3)	23.9 (27.5)	0.005 ^{a,b}
AHI 30	24 (11.0)	20 (22.7)	22 (23.4)	0.003 ^{a,b}
Sleep Questionnaire				
PSQI	6.4 (3.4)	6.5 (3.7)	8.5 (4.6)	0.002 ^{a,b,c}
ESS	8.2 (3.9)	7.8 (4.5)	9.0 (4.6)	0.12

Continuous variables are presented as means with (standard deviations). Categorical variables are expressed as frequencies and (percentages).

CKD chronic kidney disease, ESRD end-stage renal disease, BMI body mass index, eGFR estimated glomerular filtration rate, PSG polysomnography, REM rapid eye movement, PLM periodic limb movement, AHI apnea-hypopnea index, PSQI Pittsburgh Sleep Quality Index, ESS Epworth Sleepiness Scale.

[†] Chi-square or analysis of variance were used as appropriate. Reported P-values are for between group differences, P-values for subsequent pairwise comparisons are not shown.

^{*} Kruskal Wallis test

^aNon-CKD vs. CKD,

^bNon-CKD vs. ESRD,

^cCKD vs. ESRD

Table 2

Baseline blood pressure and antihypertensive use

	Non-CKD n=224	CKD n=88	ESRD n=95	P-Value[†]
SBP (mmHg)	132.2 (26.7)	148.2 (15.1)	144.5 (23.8)	<0.0001 ^{*a,b}
DBP (mmHg)	80.2 (10.3)	83.6 (13.8)	81.8 (15.6)	0.18*
Antihypertensives	0.8 (1.1)	2.8 (1.5)	1.9 (1.3)	<0.0001 ^{*a,b,c}
Resistant HTN (130/80 mmHg)	15 (6.7)	36 (40.9)	21 (22.1)	<0.0001 ^{a,b,c}
Resistant HTN (140/90 mmHg)	11 (4.9)	31 (35.2)	21 (22.1)	<0.0001 ^{a,b}

Continuous variables are presented as means with (standard deviations). Categorical variables are expressed as frequencies and (percentages).

[†] Chi-square was used as appropriate.

* Kruskal Wallis test.

^a Non-CKD vs. CKD,

^b Non-CKD vs. ESRD,

^c CKD vs. ESRD

Table 3

Associations with resistant hypertension

Variables		Unadjusted		Adjusted for Case-mix (age, gender, race, BMI, kidney function)
	N		N	
Age (per year)	404	0.99 (0.97-1.01)	402	1.01 (0.99-1.04)
Male	404	1.9 (1.1-3.3) *	402	1.7 (0.9-3.2)
African-American Race	404	1.1 (0.6-1.9)	402	2.0 (1.0-3.8) *
BMI (per kg/m ²)	402	1.02 (0.97-1.07)	402	1.05 (0.99-1.11)
Neck Circumference **	383	0.9 (0.3-2.6)	381	3.7 (0.8-16.7)
Tobacco Use (Active vs. all others)	404	1.3 (0.6-2.9)	402	0.9 (0.4-2.3)
AHI ***	397	1.7 (1.3-2.2) *	395	1.4 (1.1-1.9) *
AHI 30	397	4.0 (2.2-7.3) *	395	3.0 (1.5-6.0) *
Total Sleep Time (per hour)	399	0.82 (0.70-0.96) *	397	0.88 (0.73-1.05)
PLM Index ***	395	0.9 (0.7-1.3)	393	1.2 (0.8-1.7)
ESS Total	397	1.04 (0.97-1.1)	395	1.04 (0.97-1.1)
PSQI Total Score	374	0.99 (0.92-1.07)	373	0.97 (0.89-1.05)

BMI body mass index, AHI apnea-hypopnea index, PLM periodic limb movement, ESS

Epworth sleepiness scale, PSQI Pittsburgh sleep quality index

*
p<0.05,

**
square root transformation,

log transformation