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SLEEP APNEA IN THE GOLDEN AGE (D GOZAL, SECTION EDITOR)

Sleep Apnea and Hypertension in the Elderly

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Abstract

Purpose of Review The cardiovascular morbidity associated with obstructive sleep apnea (OSA) changes with aging. This review addresses unique aspects of OSA-associated hypertension and cardiovascular disease (CVD) in the elderly.

Recent Findings The risk of hypertension and CVD in OSA diminishes with aging. The standard apnea hypopnea index cut-offs for OSA diagnosis and severity do not predict CVD or mortality in the elderly. Further, the impact of continuous positive airway pressure (CPAP) treatment on hypertension and mortality is inconsistent in this population. A therapeutic effect of CPAP is noted in some studies in subsets of elderly with high CPAP adherence.

Summary Aging-related physiological changes in upper airway function and ventilatory control function modify the impact of OSA on hypertension and CVD. Future research should identify common endotypes of OSA and optimal OSA severity metrics from polysomnography to inform treatment algorithms for the elderly. Finally, promotion of CPAP adherence in this population may improve CVD outcomes.

Keywords Sleep apnea · Hypertension · Elderly

Introduction

The prevalence of obstructive sleep apnea (OSA) increases with age. Despite a higher prevalence in the elderly, the impact of OSA and its treatment on hypertension and cardiovascular outcomes in this population is not well understood. The evidence supports OSA as a risk factor for hypertension and some forms of cardiovascular disease (CVD) in adults. However, this association remains controversial in the elderly. The role of potential moderators of CVD risk and treatment response in the elderly with OSA needs to be defined for optimal treatment strategy. Here, we provide a narrative review of (i) the changes in OSA and hypertension risk, (ii) potential mechanisms underlying this change, and (iii) the effectiveness of OSA treatment in improving systemic blood pressure (BP) and CVD in the elderly, comparing it to middle-aged adults when applicable.

This article is part of the Topical Collection on *Sleep Apnea in the Golden Age*

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Effect of Aging on Sleep Apnea

The prevalence of OSA, defined by AHI of 15/hour or more, increases with age, likely reaching a plateau of about 20% after 60 years [1–4]. In men, the AHI increases linearly with age, while in women, the AHI rises after 50 years, approximating the prevalence of OSA in men. This increase in OSA prevalence in women is hypothetically driven by post-menopausal changes and modified by hormone replacement therapy [5, 6]. Symptoms (snoring and witnessed apnea) and obesity or central fat distribution are less predictive of OSA risk in the elderly compared to middle-aged individuals [3, 7]. Aging increases the pharyngeal collapsibility due to anatomical [8, 9] and neuromuscular changes resulting in higher upper airway resistance and lower central reflex and ventilatory motor output during sleep [10–14]. This may explain the increased propensity for apnea expression in the elderly independent of obesity.

Sleep Apnea and Hypertension in Adults

Pathophysiology

Chronic intermittent hypoxia, sleep fragmentation, and excessive intrathoracic pressure swings due to upper airway

collapse during sleep cause perturbations in autonomic function, renin angiotensin system (RAS) activation, inflammation, and oxidative stress. The pathophysiological consequences include the development of systemic hypertension, as shown in Figure 1. There is significant cross-talk between the mechanistic pathways. For example, sympathetic hyperactivity exacerbates inflammation, RAS activation, and endothelial dysfunction. RAS activation, in turn, increases fluid retention with nocturnal fluid shifts and blunts nocturnal dipping of BP. Oxidative stress and inflammatory biomarkers, such as C-reactive protein, interleukins 1,2, and 6, tumor necrosis factor alpha, and interferon gamma, are upregulated leading to permanent remodeling of the systemic vasculature [15–19]. Potential effects of aging on these pathophysiological pathways are highlighted in Figure 1 (red font).

OSA and Hypertension: Epidemiologic and Clinical Studies in Adults

Multiple clinical and community-based cohort studies have demonstrated a relationship between OSA and the risk of hypertension (Table 1). These studies adjusted for age, obesity, and the severity of OSA showed a dose-response relationship with the risk of hypertension. Overall, the association of OSA with hypertension was stronger in clinical cohorts compared to community-based cohorts. An early report from the Wisconsin Sleep Cohort showed that moderate to severe OSA was associated with more than 2.5-fold increased adjusted risk of incident hypertension after 4 years [25]. In this cohort, REM sleep–related OSA has also been noted as a risk factor for incident hypertension [33]. However, few cohorts have failed to detect a significant association between OSA and incident hypertension. A community-based longitudinal study of more than 2000 participants, age 30–70 years and followed for 7.5 years, did not find an increase in the risk of incident hypertension after adjustment for age [34]. Notable differences between this Australian cohort and the Wisconsin cohort were OSA assessment methods (type III sleep apnea test vs. polysomnography, respectively) and obesity (body mass index 25.5±3.7 vs. 27±5 kg/m^2). Hence, an underestimation of OSA and lower obesity rates may explain the negative findings reported in the study by Cano-Pumarega et al [34]. Another report on OSA and the risk of incident hypertension from the Sleep Heart Health Study found that the risk was not statistically significant after adjustment for BMI, even in the severe OSA group (odds ratio, OR=1.51, 95% confidence interval, CI=0.93–2.47) [35]. Notably, the participants' mean age in this study was 60 years compared to a mean age of 45 years in the study by Peppard et al [25].

CPAP treatment lowers sympathetic and RAS activity, which mediates BP reduction [36, 37]. In an observational study of OSA patients who were continuous positive airway pressure (CPAP) treatment users vs. non-users, Marin et al. showed that untreated OSA increased (OR 1.33–1.96) and treated OSA decreased the risk of incident hypertension (OR 0.53–0.94) compared to a control group without OSA [38]. Several recent meta-analyses have been published on the treatment effects of OSA on hypertension, as summarized in Table 1. Besides severe OSA and higher CPAP adherence, CPAP treatment's effectiveness in reducing BP is greater in symptomatic patients and those with resistant hypertension [39–41]. Some trials have failed to detect a BP response to

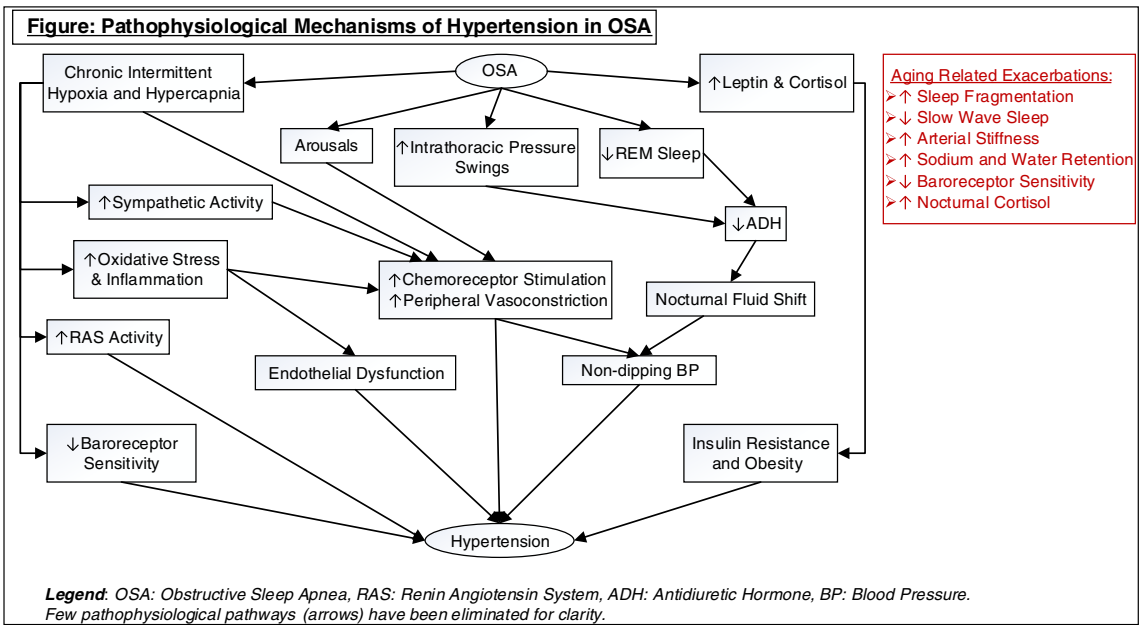

Figure 1 Pathophysiological mechanisms of hypertension in OSA. Legend: *OSA* obstructive sleep apnea, *RAS* renin angiotensin system, *ADH* antidiuretic hormone, *BP* blood pressure. Few pathophysiological pathways (arrows) have been eliminated for clarity

Table 1 Obstructive sleep apnea and hypertension: selected epidemiologic and clinical studies

Author, year	Sample	Population	Results
Cross-sectional studies			
Community cohorts			
Nieto et al, 2000 [20]	n=3670 Age ≥40 years	**OSA:** Polysomnography **HTN:** Resting BP ≥140/90 mmHg, not on BP medications	•For AHI≥30, OR= 1.37 (CI 1.03–1.83) •**In age≥65 sub-group, OR= 1.23 (CI 0.83-1.83)**
Bixler et al, 2000 [21]	n=1741, sub-selected based on risk factors for OSA, age 20–88 years	**OSA**: Polysomnography **HTN:** Resting BP ≥140/90 mmHg or on BP medications	•For AHI≥15, OR= 1.72 (CI 1.24–2.55). **The OR was not increased in age ≥65 years**
Clinical populations			
Lavie et al, 2000 [22]	n=2677 Age 20–85 years	**OSA**: In-lab respiratory flow and effort measurement **HTN:** Resting BP ≥140/90 mmHg	•↑ AHI of 10/hour = 11% ↑ odds of HTN (CI 0.07–0.15).
Grote et al, 1999 [23]	n=1,642 Age 20–88 years	**OSA**: Pulse oximetry and snoring **HTN:** History or medication use. Resting BP measured in those without HTN (n=591).	•For AHI≥40, OR of BP≥140/90 mmHg = 1.93 (CI 1.1–3.3) and OR of BP≥160/95 mmHg = 4.15 (CI 2.7–6.5) •For AHI≥40 and ≤50 years of age, OR of BP≥160/95 mmHg = 7.15 (CI 3.8–13.6) vs. **in >50-year group, OR= 2.7 (CI 1.4-5.1).**
Haas et al, 2005 [24]	n=6120 Age 40–59 years, n=2477 Age≥60 years, n=3643	**OSA**: Polysomnography **HTN:** Resting BP ≥140/90 mmHg or isolated systolic HTN, resting BP ≥140 and <90 mmHg	•For age 40–59 and AHI ≥5, OR of isolated systolic HTN was 1.49 (CI 1.02–2.17) and HTN 1.61 (CI 1.04–2.47) •**No increased risk of isolated systolic HTN or HTN in any AHI category noted in ≥60-year group**
Longitudinal studies			
Community cohort			
Peppard et al, 2000 [25]	n=709 Mean age 45 years	**OSA**: Polysomnography **HTN:** Resting BP ≥140/90 mmHg	•Dose response relationship between baseline AHI and BP at 4-year follow-up. For AHI ≥15, OR = 2.89 of HTN after adjustment for BMI (95% CI 1.46–5.64)
Interventional studies			
Clinical trials & meta-analyses			
McMillan et al, 2014 [26]	n=278, RCT **Age≥65 years**	**OSA**: ODI 4%>7.5/hour **HTN:** Systolic and diastolic BP, secondary outcomes at 3 and 12 months	•No effect of auto-titrating CPAP on BP
Martinez-Garcia et al, 2015 [27]	n=224, RCT **Age≥70 years**	**OSA:** AHI≥30/hour **HTN:** Office BP	•No effect of CPAP on BP
Ponce et al, 2019 [28]	n=145, RCT **Age≥70 years**	**OSA**: AHI 15-30/hour **HTN:** Office BP, secondary outcome at 3 months	•No effect of CPAP on BP
Bakker et al, 2014 [29]	Meta-analysis Eight RCTs	**Intervention**: CPAP **HTN**: 24-h BP or clinic BP	•Systolic BP reduction of −2.27 (95% CI −4.01 to −0.54) and diastolic BP of −1.78 mmHg (95% CI −2.99 to −0.58) •Uncontrolled HTN: Systolic BP reduction of −7.1 and diastolic BP of −4.3 mmHg
Fava et al, 2014 [30]	Meta-analysis Thirty-one RCTs	**Intervention**: CPAP **HTN**: 24-h BP or clinic BP	•Systolic BP reduction of 2.2±0.7 (day) and 3.8±0.8 (night) •Diastolic BP reduction of 1.9±0.6 mmHg (day) and 1.8±0.6 mmHg (night)

Table 1 (continued)

Author, year	Sample	Population	Results
Iftikhar et al, 2013 [31]	Meta-analysis Seven studies Observational & RCTs	**Intervention**: Oral Appliance **HTN**: 24-hour BP or clinic BP	• •Systolic BP reduction of −2.7 mmHg (CI −0.8 to −4.6) and diastolic BP reduction by −2.7 mmHg (CI −0.9 to −4.6)
Iftikhar et al, 2014 [32]	Meta-analysis Six studies Observational & RCTs	**Intervention**: CPAP **Resistant HTN**: 24-h BP	•BP reduction of −7.21 mmHg (CI −9.04 to −5.38) and diastolic BP reduction by −4.99 mmHg (CI −6.01 to −3.96)

Legend: *OSA* obstructive sleep apnea, *HTN* hypertension, *BP* blood pressure, *AHI* apnea hypopnea index, *BMI* body mass index, *OR* odds ratio, *CI* confidence interval, *RCT* randomized controlled trial, *CPAP* continuous positive airway pressure, *ODI* oxygen desaturation index

*OR presented from models adjusted for age, obesity, and other covariates. Specific studies and findings in the elderly are highlighted in bold font.

CPAP treatment, likely due to the abovementioned moderators of CPAP treatment effects [42–45]. Overall, CPAP effects on BP are less than some antihypertension medications [46].

Sleep Apnea and Hypertension in Elderly

The strength of the evidence supporting OSA as an independent risk factor for hypertension is weaker in the elderly compared to middle-aged adults. In the Sleep Heart Health Study, the risk for hypertension in the severe OSA group (AHI ≥30) over 65 years of age was 23% higher but statistically insignificant compared to the control group without OSA. However, a significant 64% increased risk of hypertension was noted in the middle-aged severe OSA group [20]. Another report from the same cohort found no association of OSA with isolated systolic hypertension, which is more prevalent in the elderly [24]. In contrast, a study from France in the elderly found a significant increase in systolic ambulatory and diastolic nocturnal BP in the severe OSA group compared to those without OSA [47]. Follow-up reports from the same group found that severe OSA conferred an 80% higher risk of incident hypertension after 3 years [48], and the oxygen desaturation index (ODI) was a significant predictor of elevated daytime ambulatory BP [49]. Sex differences in the risk of hypertension related to OSA may exist, with studies suggesting a higher risk only in women [50, 51]. Population differences in sex, obesity, and other moderators of the OSA-hypertension association may account for the disparate findings in the elderly.

Few trials have examined the effects of CPAP intervention specifically in the elderly. CPAP improves the quality of life, symptoms, mood, and neurocognitive function and is cost-effective in this population [26, 27]. However, as summarized in Table 1, CPAP treatment does not significantly reduce BP in the elderly [26, 28].

Does Sleep Apnea or CPAP Treatment Impact Cardiovascular Disease and Mortality in the Elderly?

Prospective cohorts have reported that severe OSA confers an increased risk of cerebrovascular disease (CVA) in the elderly, but not coronary heart disease (CHD) [52–54]. Further, sex differences are reported in the risk of CVD associated with OSA in the elderly. A prospective cohort of women aged 65 years or more with untreated OSA did not demonstrate a significant increase in CVA or CHD risk compared to those without OSA [55]. In a small, single-center study, OSA increased the risk of arrhythmia and cardiovascular events 6 months after acute myocardial infarction in the elderly [56]. Another report from a post-acute coronary syndrome sample of patients enrolled in a cardiac rehabilitation program found that OSA was associated with diastolic dysfunction in those less than 60 but not in the group over 60 years of age [57].

Similarly, early studies demonstrated that the association between OSA and mortality is attenuated with aging [58, 59]. In a study of over fourteen-thousand adult men, aged 20–93 years with suspected or diagnosed OSA, those aged ≥ 50 years did not have excess all-cause mortality compared to the general population [60]. Another study of over three-thousand men followed for 10 years reported an increase in overall and cardiovascular mortality in those with symptoms of OSA (versus those without symptoms) in the <60-year group but not in the ≥ 60-year group [61]. In the Sleep Heart Health Study, all-cause mortality in severe OSA was 46% higher than those without OSA. Further age and sex stratifications revealed that the increased mortality was driven by men ≤ 70 years (adjusted hazard ratio 2.09, CI 1.31–3.33) [62]. In contrast, OSA *with daytime sleepiness* was shown to increase the mortality risk 2.3-fold in an elderly cohort followed for more than 13 years, after adjustment for other risk factors such as sex and sleep duration [63]. Another factor that may impact the association of OSA with mortality in the elderly is the hypopnea definition used to diagnose OSA. When hypopnea is defined by oxygen desaturation alone, without considering arousals, severe OSA is associated with a significant and more than 2-fold increase in cardiovascular mortality in the elderly [64]. This is not surprising, since sleep fragmentation with aging is common and multifactorial.

Regarding CPAP treatment effects, a retrospective analysis of Medicare beneficiaries (≥ 65 years) with CPAP-treated OSA and followed for 25 months showed a 2% reduction in risk of CVA attributable to each month of CPAP use [65]. A prospective study on 166 CVA patients followed for 5 years (mean age 73 years, 96 with AHI≥20/hour) after hospitalization for ischemic CVA showed that patients with untreated OSA had increased mortality (HR, 1.58; 95% CI, 1.01–2.49) compared to those treated with CPAP [66]. In the elderly with moderate to severe OSA, CPAP treatment of more than 4 h nightly improves survival compared to untreated OSA [67, 68]. Many observational studies did not assess CPAP adherence, and low treatment adherence is a particular concern amongst the elderly [69, 70]. The importance of CPAP adherence is underscored in an observational study of 939 patients, 65 years or more of age with OSA, followed for 10 years. The mortality was significantly increased by 120% in the group with untreated severe OSA (AHI≥30/hour) compared to those with AHI <15/hour [27]. Notably, CPAP adherence was a significant predictor of change in cardiovascular mortality in the treated group. Consistent with the results discussed above, a meta-analysis by Kim et al, showed that the observational studies suggested a significant reduction in the risk of CVA (Relative Risk, RR=0.27, CI 0.14-0.53) and cardiac events (RR=0.54, CI 0.38-0.75). Howwever, these trends were not confirmed by the randomized trials included in this meta-analysis, except in the subgroup with high CPAP adherence [71].

Conclusions

OSA appears to play a lesser role in propagating hypertension and CVD in the elderly compared to middle-aged adults. This may be due to survival bias or ischemic preconditioning of cardiovascular tissues caused by chronic intermittent hypoxia in OSA. Nevertheless, factors such as sex, obesity, symptoms, comorbidity, assessment methods, and definition of OSA influence the association of OSA with hypertension and CVD. These factors require systematic examination in adequately powered prospective studies. The endotypes of OSA may further affect CVD risk and treatment response in the elderly with OSA and merit further investigation [72]. Finally, CPAP adherence is a crucial determinant of CPAP treatment response in the elderly. Clinical trials in the elderly, promoting and controlling for CPAP adherence, are urgently needed.

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Declarations

Conflict of Interest The authors do not have any conflict of interest.

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- • Of importance
- •• Of major importance

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