



Hypertension and Cognitive Decline: Implications of Obstructive Sleep Apnea

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Hypertension and dementia are highly prevalent in the general population. Hypertension has been shown to be a risk factor for Alzheimer's dementia and vascular dementia. Sleep apnea, another common disorder, is strongly associated with hypertension and recent evidence suggests that it may also be linked with cognitive decline and dementia. It is possible that sleep apnea is the final common pathway linking hypertension to the development of dementia. This hypothesis merits further exploration as sleep apnea is readily treatable and such therapy could foreseeably delay or prevent the onset of dementia. At present, there is a paucity of therapeutic modalities that can prevent or arrest cognitive decline. In this review, we describe the associations between hypertension, dementia and sleep apnea, the pathophysiologic mechanisms underlying these associations, and the literature examining the impact of treatment of hypertension and sleep apnea on cognition. Potential areas of future investigation that may help advance our understanding of the magnitude and direction of the interaction between these conditions and the effects of treatment of high blood pressure and sleep apnea on cognition are highlighted.

Keywords: blood pressure, dementia, sleep apnea, sleep deprivation, insufficient sleep, insomnia, sleepiness, somnolence

INTRODUCTION

Hypertension has recently been recognized as a risk factor for cognitive decline/dementia (1, 2). Both hypertension and cognitive decline/dementia are commonly seen in the general population (3, 4). A significant number of individuals with hypertension remain untreated, likely increasing their risk of long-term negative health consequences (3). Alzheimer's disease (AD) and vascular dementia account for the majority of the cases of dementia and most individuals with dementia have a combination of these two pathologies (5, 6). AD is the most common cause of dementia; it is a neurodegenerative disease, generally of older age, that is associated with excessive deposition of neurofibrillary tangles and amyloid plaques (7, 8). Vascular dementia is the second most common type of dementia accounting for 25–50% of all cases and refers to dementia in which cerebrovascular or cardiovascular disease is a primary cause or contributing factor (6, 9). Cardiovascular diseases, including hypertension, are risk factors for the development of AD as well as vascular dementia (6, 10). Additionally, cardiovascular diseases, AD and vascular dementia are thought to have shared genetic underpinnings and pathophysiology (11, 12).

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Sleep disordered breathing or sleep apnea is also highly prevalent in the general population and is associated with several adverse cardiovascular outcomes (13–17). In its most common form, namely, obstructive sleep apnea (OSA), partial, or complete upper airway closure occurs during sleep in a repetitive fashion leading to hypoxemia and sleep fragmentation (18). OSA has been linked to incident and prevalent hypertension in several studies and it is thought that sympathetic overactivity leads to the development of high blood pressure (BP) in these individuals (19, 20). A growing body of evidence suggests that OSA is associated with cognitive impairment and dementia (21). It is possible that OSA plays a contributory role in the increased risk of cognitive decline and dementia seen in subjects with hypertension.

In this brief review, we describe the associations between hypertension and cognitive decline/dementia, between sleep apnea and hypertension, as well as between sleep apnea and cognitive decline/dementia. We discuss the putative pathophysiologic mechanisms underlying these associations. We also examine the literature assessing the effects of treatment of hypertension on cognitive function and the treatment of sleep apnea on BP and cognition. Last, we highlight areas of future investigation that may improve our understanding of the relationship between hypertension and sleep apnea as it pertains to the risk of cognitive decline/dementia, and the potential clinical impact of treatment of these conditions on the prevention of onset or worsening of cognitive decline.

HYPERTENSION AND COGNITIVE DECLINE/DEMENTIA

Epidemiology

Hypertension has been shown to be associated with cognitive decline, AD and vascular dementia (1, 2). Several large epidemiologic studies have demonstrated a link between high BP in midlife (4th–5th decades of life) and cognitive decline or AD in later life, i.e., in the subsequent 20–30 years (19–23). This association has been more consistently established for diastolic BP (DBP) than systolic BP (SBP) (22, 23). A few investigations specifically assessing the relationship between midlife hypertension and vascular dementia have also found a significant association (4, 23). **Supplementary Table S1** shows a summary of the epidemiologic studies examining the association between midlife elevated BP and cognitive decline/dementia.

The duration of high BP and the trajectory of BP over time appear to significantly influence the risk of cognitive decline/dementia (24, 25). Early-onset hypertension in childhood, adolescence or young adulthood, and duration of high SBP exceeding 25–30 years significantly enhances the risk, as does a combination of elevated BP in midlife coupled with low DBP in late-life (24–26). This is especially concerning, given that the prevalence of hypertension in younger individuals has been increasing steadily in the general population (27). Increased 24-h mean BP, 24-h variability of BP and non-dipping BP at night have all been associated with increased risk of cognitive impairment in those with and without hypertension (28–30). Interestingly, non-dipping of BP is extremely common

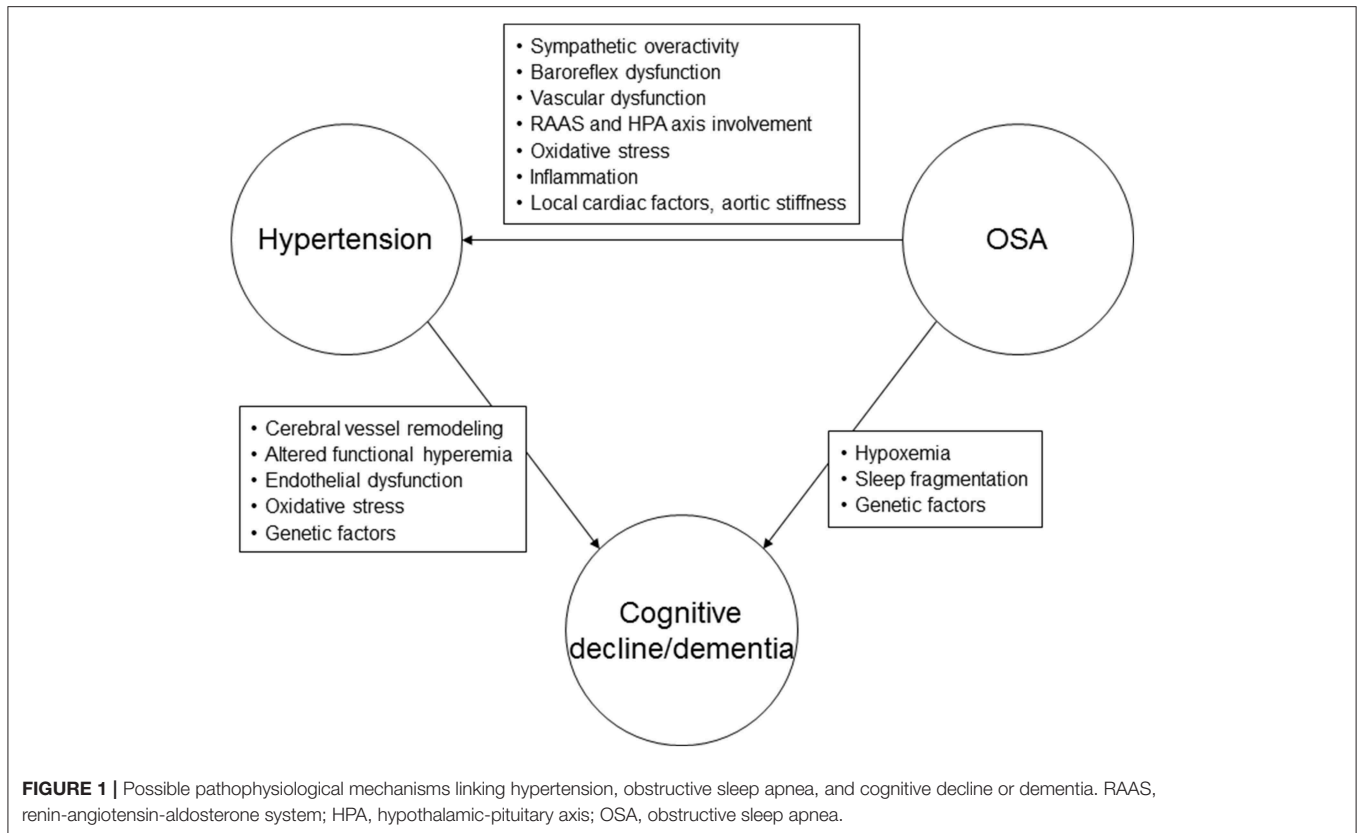
in individuals with OSA and is discussed in more detail in the next section.

The association between late-life high BP and incident cognitive decline/dementia, both AD, and vascular dementia, is not consistent across studies (1). Hypertension in the 6th–7th decades of life has been linked with cognitive decline and a diagnosis of mild cognitive impairment (MCI) (31, 32). However, hypertension in the 8th–10th decades has not been found to increase such risk, and there are some data to suggest that it may in fact be protective against the development of cognitive impairment, especially in those with pre-existing chronic hypertension (33–35). This may in part reflect selection bias, in that those who do not develop cognitive impairment after many years are in a sense “resistant” to it. It is notable that in elderly individuals, low BP, very high SBP of >160 mm Hg and increased blood pressure variability have all been linked to cognitive impairment (36–39).

Mechanisms

Our understanding regarding the mechanisms underlying cognitive dysfunction in hypertension has recently been enhanced by advances in neuroimaging, which have consistently demonstrated effects of hypertension on brain structure and function. Increased SBP has been associated with reduced regional and total brain volumes, with further reductions in volume noted over time (40–42). The association between elevated DBP and brain volumes is not as clear (41–43). One of the main mechanisms underlying cognitive dysfunction in hypertension appears to involve cerebral vessel remodeling, leading to changes in cerebral autoregulation and perfusion, and thus affecting the ability to clear beta-amyloid (44) (**Figure 1**). Altered functional hyperemia, endothelial dysfunction and oxidative stress are other mechanisms that may play a contributory role (1). Subjects with hypertension demonstrate more beta-amyloid plaques, neurofibrillary tangles and cerebral atrophy compared to normotensive individuals (45–47). Subjects with hypertension also have reduced glucose metabolism in specific regions of the brain (47). Genetic variants may influence the effects of high BP on cognitive function. It appears that individuals with abnormal beta-amyloid levels and high midlife BP are at significantly increased risk of AD in the future (48). Some investigations have demonstrated that hypertension is linked to the development of cognitive impairment in subjects with the Apolipoprotein ϵ 4 (APOE4) allele (48, 49).

Hypertension has been noted to be associated with the hallmark features of vascular dementia on neuroimaging studies, with reduced white matter microstructural integrity noted even prior to the development of overt neuroimaging abnormalities (50–53). The cognitive domains most affected by hypertension appear to be executive functioning and information processing speed (54, 55). There is accumulating evidence to suggest that treatment of hypertension decreases white matter hyperintensity progression (42, 52, 56). However, the relationship between hypertension and brain health is still not fully understood and can be affected by many factors including age, duration and trajectory of hypertension, as well as the degree of efficacy of antihypertensive medication.



Treatment Effects Findings

Prior randomized controlled trials evaluating the effects of antihypertensive treatment on cognitive function have shown mixed results (2). There was no convincing evidence of reduction in risk of cognitive decline in two placebo-controlled randomized controlled trials evaluating the effects of renin-angiotensin system blockade on cognitive function in subjects at high risk of cardiovascular disease (57, 58). A Cochrane systematic review also found no evidence that lowering of BP in late life reduced the risk of cognitive decline/dementia in hypertensive subjects (58). In the SPRINT MIND study, treating ambulatory adults with hypertension to a goal SBP of <120 mmHg compared to <140 mm Hg did not result in significant decrease in the risk of probable dementia after a mean follow-up of close to 6 years (59). However, there was a statistically significant reduction in risk of MCI (hazard ratio, 0.81, 95% CI, 0.69–0.95) noted in this study. A recent study showed that race may moderate of the impact of BP control on cognitive function (60). Results of other studies examining the impact of more intensive control of hypertension on cognitive function/risk of dementia are conflicting (59, 61). There is also evidence that excessive lowering of nocturnal BP may itself contribute to changes that may predispose to risk of dementia (62, 63). Amongst antihypertensive medications, it appears that angiotensin receptor blockers (ARBs) may be superior to other agents in decreasing the risk of cognitive decline/dementia according to a recent meta-analysis; however, this may be related to the possible neuroprotective effect

of ARBs themselves rather than due to a reduction in BP (64).

Limitations

It remains uncertain if treatment of hypertension can change the course of cognitive decline/dementia. Several studies examining the effects of antihypertensive treatment on cognitive function had short durations of follow up. Additionally, many control subjects in the studies included in the Cochrane systematic review received antihypertensive treatment (58). The SPRINT MIND study was terminated early and there were fewer than expected cases of dementia, hence the study may have been underpowered to detect this endpoint (59, 65). Finally, most previous studies used the mini-mental state examination which has significant limitations in assessing cognitive outcomes (66).

Future Directions

Future studies should account for the shortcomings listed above and consider utilizing dementia-specific biomarkers as early indicators of cognitive decline and/or treatment-related effects, although is noteworthy that the use of biomarkers for this purpose has been debated in the literature (1, 67). Future investigations should consider the use of more comprehensive neurocognitive batteries for testing (66). The use of alternate markers of vessel function e.g., pulse pressure may provide further insights into the mechanisms underlying risk of cognitive decline/dementia in those with hypertension (1, 68, 69). The effects of varying degrees of BP control and the threshold below

which BP needs to be lowered in order to improve neurocognitive outcomes needs clarification. Finally, the impact of BP reduction with antihypertensive medication on cognitive decline/dementia in various age, sex, ethnic, genetic, and clinical subgroups with hypertension requires further study (38, 69, 70).

SLEEP APNEA AND HYPERTENSION

Epidemiology

Sleep apnea and hypertension are closely linked conditions, with shared risk factors such as age, male sex, and obesity (71). OSA is estimated to affect up to 24% of adult males and 9% of adult females in the United States (13). About half of subjects with hypertension have coexisting OSA and conversely, half of those with OSA have hypertension (72, 73).

Rapid eye movement (REM)-related OSA, a type of OSA in which disordered breathing events are mainly seen in REM sleep, has been independently associated with incident and prevalent hypertension (74, 75). Additionally, up to 80% of individuals with OSA demonstrate a non-dipping BP pattern at night; i.e., their BP does not demonstrate the normal physiological drop that occurs during sleep (76–78). Non-dipping BP status is a negative prognostic indicator, associated with increased risk of microalbuminuria, left ventricular hypertrophy, and cardiovascular morbidity and mortality. Very short-term (beat-by-beat) variability of BP is also related to severity of OSA, may be a negative cardiovascular prognostic indicator and amenable to treatment of OSA (79). Several recent studies have focused on the relationship between OSA and resistant hypertension (80–82). Approximately 70% of subjects with resistant hypertension have underlying OSA (80, 81). The increased risk of resistant hypertension in OSA appears to be particularly prominent in African-Americans, in whom undiagnosed OSA tends to be a highly prevalent condition (83, 84).

Mechanisms

The mechanisms underlying hypertension in sleep apnea are thought to predominantly involve the chemoreflex response to hypoxemia (81, 85) (Figure 1). Impaired baroreflex responses, vascular dysfunction, systemic inflammation, and renin-angiotensin-aldosterone system involvement are other pathophysiologic mechanisms that may lead to elevated BP in subjects with OSA (81).

Treatment Effects

Findings

The impact of treatment of OSA in lowering BP is modest, with a reduction in mean 24-h SBP and DBP of approximately 2–4 mm Hg (20, 86). The BP lowering effects of CPAP are noted in subjects with pre-hypertension and hypertension, and appear to be greater in those with a higher number of hours of device usage and those who are sleepy, comorbid diabetes mellitus, and possibly in those using fixed vs. auto-titrating modes of PAP (87, 88). Studies have suggested that CPAP treatment may reverse non-dipping of BP at night in those with resistant hypertension (89, 90). The magnitude of reduction in BP with CPAP therapy for OSA appears to be greater in those with

resistant hypertension, in the range of 5–7 mm Hg for SBP and 3–6 mmHg for DBP (90–92). A recent study demonstrated that a cluster of micro-ribonucleic acids predicted a reduction in BP with CPAP (93). Another recent review described the potential role of mineralocorticoid antagonists in the treatment of resistant hypertension and decreasing the severity of SDB in subjects with OSA (94). Renal denervation has also been shown to decrease the severity of sleep apnea in subjects with resistant hypertension in a recent proof-of-concept randomized controlled trial (95).

Limitations

Studies evaluating the effects of treatment of OSA on BP have utilized varying methods of measurements of BP and have included differing populations with hypertension, some on antihypertensive medication(s), making it difficult to compare results across studies.

Future Directions

Further investigations are required to determine whether 24-h or beat-by-beat variability in BP can lead to the development of cognitive decline/dementia in subjects with OSA, with or without coexisting hypertension, and whether treatment of OSA can ameliorate this risk. Future randomized controlled trials are required to assess the benefit of treatment of OSA in preventing the development of incident hypertension. Studies are also needed to clarify the comparative effects of various treatment modalities for sleep apnea on BP and the differential effects of treatment in various subpopulations of those with OSA, such as those with REM-related OSA, those with excessive daytime sleepiness, and in various ethnic subgroups.

SLEEP APNEA AND COGNITIVE DECLINE/DEMENTIA

Epidemiology

There is a growing body of literature suggesting an association between sleep apnea and cognitive decline, particularly in elderly individuals (21, 96). Much of the evidence comes from population-based studies and there are some negative studies in this regard as well. As with the studies evaluating the relationship between sleep apnea and hypertension, varying methods of assessing sleep apnea and cognitive function utilized in the different studies render it challenging to compare results and make definitive conclusions about the association between sleep apnea and cognitive decline/dementia.

A recent meta-analysis conducted by Leng and colleagues included cross-sectional and longitudinal population-based studies with a minimum of 200 participants each, mean age of 40 years or older, in whom cognitive dysfunction was assessed based on a clinical diagnosis of cognitive impairment or by using standard tests (21). Sleep apnea was considered to be present if the AHI was 15 events per h or greater. Fourteen studies including 4 million male and female subjects from 5 different countries showed that sleep apnea was associated with an increased risk of cognitive impairment. The risk ratio for cognitive impairment in those with sleep apnea from the pooled analysis of 6 longitudinal studies was 1.26 (95% CI 1.05–1.50)

and from 5 longitudinal studies (after removing 1 study that introduced significant heterogeneity) was 1.35 (95% CI 1.11–1.65). Pooled analysis from 7 cross-sectional studies revealed that those with sleep apnea exhibited a small worsening of executive functioning (standard mean difference -0.05 , 95% CI -0.09 – 0.00). There was no association noted between sleep apnea and global cognition (6 studies) or delayed memory (5 studies) in pooled analyses from the cross-sectional studies in which these outcomes were available. No evidence of publication bias was found by the authors. Similar findings regarding the effects of sleep apnea on specific cognitive domains have been noted in other meta-analyses of studies conducted in clinical populations (97, 98). A previous meta-analysis of case-control studies showed that individuals with AD were five times more likely to have sleep apnea than subjects of the same age who were cognitively intact (99).

Mechanisms

The mechanisms underlying the association between sleep apnea and cognitive impairment are not fully understood at this time, but may include hypoxemia, sleep fragmentation, daytime sleepiness, amyloid, and tau protein neuropathology, oxidative stress, inflammation and metabolic dysfunction (99–104) (**Figure 1**). Both insufficient sleep (including insomnia) and excessive daytime sleepiness have been linked with dementia (96). From large population-based cohorts of subjects with OSA it appears that hypoxemia, in particular, the degree of nocturnal desaturation, may be more important as a possible causative factor for cognitive decline/dementia than sleep fragmentation (105, 106). Chronic intermittent hypoxemia may result in vascular dysfunction, neuronal damage and impairment of the blood-brain barrier, affecting synaptic plasticity (107). Multiple structural brain abnormalities have been described in subjects with OSA, including white matter hyperintensities, cerebral microbleeds, perivascular spaces, and gray matter changes in the form of reduced cortical thickness in the temporal areas that were found to be associated with decreased verbal encoding on neuropsychological testing (108–111).

Studies have indicated that the effects of sleep apnea on cognition are more pronounced in APOE4 gene carriers and it may be that the presence of this genotype confers an increased risk of cellular damage from oxidative stress and promotes neural inflammation (112, 113). OSA may lead to early changes in the biomarkers of AD, which are potentially modifiable (102, 114). These include a wide array of cerebrospinal fluid and blood biomarkers such as amyloid- β , tau proteins, inflammatory cytokines, acute-phase proteins, antioxidants, homocysteine, and clusterin (102, 115, 116).

Treatment Effects Findings

The effects of treatment of OSA on cognitive function are unclear at this time, with only slight, and inconsistent improvements noted in the various measures of neurocognitive function utilized in the studies that did show benefit following treatment of OSA (117–119). A recent pilot study demonstrated significant improvements in psychomotor/cognitive processing speed in

subjects with MCI who were adherent to CPAP for a year compared to subjects with MCI and OSA who were not adherent to CPAP treatment (120). Both the CPAP-adherent and non-adherent group had similar rates of hypertension.

Limitations

Several of the above studies evaluating the effect of sleep apnea on cognition did not specifically examine BP as a contributory factor. The presence and contribution of underlying sleep disorders to the symptoms and risk of dementia have not been elucidated.

Future Directions

Further studies are required to explore mechanisms underlying cognitive dysfunction in sleep apnea; in particular, the influence of hypoxemia vs. sleep fragmentation and genotypes that might predispose individuals to the development of cognitive impairment/dementia. Large cohort studies are required to help identify a specific biomarker panel associating sleep apnea with the risk of dementia. Studies utilizing more comprehensive neurophysiologic test batteries to understand the effects of SDB on specific cognitive domains are needed. The outcomes need to be defined more clearly, i.e., the presence of mild cognitive impairment vs. dementia or cognitive decline, ascertained by changes in measures on serial testing, need to be classified as different outcomes. Analyses of neurocognitive outcomes by various age groups are required to help stratify risk, as well as those that account for the influence of potential confounders such as body mass index, as noted by Leng et al. (21). Also noted by the authors of this meta-analysis, studies using AHI as a continuous variable rather than as a dichotomized measure to assess for the risk of sleep apnea on cognition are needed; additionally, differing hypopnea definitions utilizing varying oxyhemoglobin and/or arousal criteria can yield very different AHI values; thus, standardization of criteria measuring the severity of sleep apnea are required when assessing its impact on cognitive outcomes.

CONCLUSIONS

Hypertension, cognitive impairment and sleep apnea are common in the general population. Recent literature points to an association between hypertension and cognitive impairment/dementia. The link between sleep apnea and hypertension has been well described and the pathophysiologic mechanisms underlying this relationship have been studied in human subjects. Sleep apnea has also been identified as a risk factor for cognitive impairment and dementia, but the mechanisms underlying this relationship have not been completely delineated. It is conceivable that sleep apnea provides a pathway connecting hypertension to the onset of cognitive decline or dementia. Alternatively, the repetitive nocturnal hypoxemia associated with sleep apnea may conceivably serve to potentiate effects of hypertension on cognitive decline/dementia, and/or increased blood pressure may conceivably potentiate the effects of sleep apnea on risk of dementia. While sleep apnea may not fully account for the development of cognitive impairment or dementia in those with hypertension, it may

serve to heighten the risk in vulnerable individuals. This hypothesis merits further exploration given that sleep apnea is an eminently treatable condition and the relative lack of interventions that are currently available for the prevention or treatment of cognitive decline/dementia. Identification of sleep apnea, particularly in elderly individuals, may help predict the risk of cognitive impairment. Based on the current evidence, perhaps those with moderate to severe SDB should be closely followed in the clinical setting for occurrence of cognitive dysfunction, with consideration given to full neuropsychometric testing for early detection of cognitive impairment. There is limited evidence that treatment of OSA may help cognition and the results of studies are conflicting. Future studies are urgently needed to evaluate whether treatment of sleep apnea can help reverse cognitive deficits and delay or prevent the onset of dementia.

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MM and BK wrote the manuscript. VS provided critical review and made changes to the manuscript.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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