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SLEEP AND HYPERTENSION (S JUSTIN THOMAS, SECTION EDITOR)

Sleep and Resistant Hypertension

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Abstract

Purpose of Review The goal of the present review is to describe the current findings on the association of sleep with resistant hypertension (hypertension that remains uncontrolled despite the use of three or more antihypertensive medications from different classes, including a diuretic).

Recent Findings Sleep disturbances, particularly obstructive sleep apnea (OSA), are highly prevalent among adults who have resistant hypertension. Randomized controlled trials indicate that treating OSA has modest effects on blood pressure lowering among those with the highest initial blood pressure. There is a paucity of research on the association of habitual sleep and other sleep disturbances with resistant hypertension. Of note, the most recent observational studies describing the association of OSA with resistant hypertension are comprised primarily of non-white race/ethnic groups who are far more likely to have resistant hypertension.

Summary OSA is associated with resistant hypertension, but there is limited data on associations between sleep characteristics and resistant hypertension. Future studies should investigate whether treating OSA can reduce disparities in resistant hypertension and whether other aspects of sleep also contribute to resistant hypertension.

Keywords Sleep · Obstructive sleep apnea · Racial/ethnic disparities · Hypertension

Introduction

Hypertension is the leading modifiable cause of death worldwide. In the USA, hypertension is the most common medical diagnosis, affecting 75 million adults. Over half of all adults with hypertension (54.2%) do not achieve target levels of systolic blood pressure ≤ 130 mmHg and diastolic blood pressure ≤ 80 mmHg [1••]. Treatment-resistant hypertension, defined as an above goal blood pressure despite the use of three antihypertensive agents from different drug classes (including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system, and a diuretic) or a controlled blood pressure with four or more medications [2, 3•], is estimated to affect 10.3% of adults worldwide [4] and 19.7% of adults in the USA [1••].

Hypertension becomes "refractory" when blood pressure remains uncontrolled despite maximal therapy, commonly defined as the use of five or more antihypertensive medications including chlorthalidone and spironolactone. The prevalence of refractory hypertension is difficult to capture, but at least one US-based study identified refractory hypertension among 10% of patients who were referred to a specialty clinic for resistant hypertension [5]. All forms of treatment-resistant hypertension damages target organs including the cerebral vessels, kidney, and the heart leading directly to the development of myocardial infarction, stroke [6], chronic kidney disease [7, 8], and heart failure.

There are significant racial/ethnic disparities in resistant and refractory hypertensions that pattern established disparities in hypertension prevalence and control, whereby the highest rates are observed among non-whites [9]. Studies using the 2008 hypertension definition identified higher rates of resistant and refractory hypertension among non-white

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groups including non-Hispanic blacks, Native American Indians/Alaskan Natives, Puerto Ricans, South Asians, and Filipinos as compared with non-Hispanic whites [10, 11]. However, resistant and refractory hypertensions are most common among non-Hispanic blacks with a prevalence of 27.3% vs. 18.9% in non-Hispanic whites and 17.7% among Mexican-Americans [1••].

Although pharmacologic management forms the cornerstone of hypertension management, lifestyle change is equally critical. Health behaviors that promote weight loss such as physical activity and hypocaloric diets directly address obesity which underlies many cases of hypertension and influences its control. However, other lifestyle behaviors including sodium restriction, smoking cessation, moderate alcohol consumption, and treatment of obstructive sleep apnea (OSA) are also highlighted as strategies to promote blood pressure control [12–14].

Sleep health is fundamental to mental and physical health, and when disrupted, it poses a significant public health burden [15, 16]. With the exception of OSA, sleep disorders have received relatively little attention in resistant hypertension. Current clinical recommendations are to evaluate all treatment-resistant patients with hypertension for apnea and to initiate therapies for OSA (e.g., continuous positive airway pressure (CPAP)) when indicated [17–19]. Treating OSA may have wide-ranging benefits since doing so can improve sleep quality and duration, which may influence other lifestyle targets such as adherence to diet and medical recommendations [20, 21].

The objective of the present review is to describe the state of the science relating sleep and circadian disturbances with treatment-resistant hypertension. A prior review of the topic was carried out in 2014 [22]. The current review highlights new evidence since that time, ending with recommendations for future directions.

Association of Obstructive Sleep Apnea with Treatment-Resistant Hypertension

Epidemiological and clinical studies report a positive association between OSA and resistant hypertension that is described in the summary provided by Marcus and colleagues up through 2014 [22]. They additionally discuss the results of clinical trials that demonstrated that treating OSA is associated with improved blood pressure control in specific situations.

Observational Studies

Cross-sectional studies report a high prevalence (60–71%) of OSA among patients with resistant hypertension [19, 23], with an even stronger association among black patients with resistant hypertension [24]. Of note, the use of a diuretic in the treatment of hypertension, specifically spironolactone, has been shown to decrease apnea severity, likely through volume reduction. On the basis of these observations, the 2017 hypertension guidelines reference OSA as a secondary contributor to hypertension and recommend screening for patients with resistant or refractory hypertension for OSA [25].

Since the 2014 review, there have been two new original research manuscripts that focused on the relationship of sleep with resistant hypertension [26••, 27••]. In a study by Bhanderi and colleagues [26••], Kaiser Permanente Southern California members with hypertension and OSA, identified based on physician diagnosis codes 327.2, 327.21, 327.23, 780.51, 780.53, and 780.57 or coding for dispensation of apnea treatment devices between 2006 and 2010, were included in a retrospective analysis. Investigators determined the odds of having resistant hypertension as compared with controlled hypertension between those with and without OSA. There were 33,682 diagnoses of sleep apnea among the 470,386 Kaiser plan members with hypertension.

Following statistical adjustment for confounders including age, sex, race, BMI, and medical comorbidities, an OSA diagnosis was associated with a significantly higher likelihood of having resistant hypertension (odds ratio = 1.16, 95% CI 1.12–1.19). The investigators additionally observed that those participants who had OSA and resistant hypertension were significantly more likely to experience ischemic heart disease events (HR = 1.24, 95% CI 1.13 to 1.35) and heart failure (HR = 1.43, 95% CI 1.28 to 1.61) during follow-up as compared with those who did not have resistant hypertension [26••].

The second new study since the last review by Johnson et al. [27••] tested the cross-sectional association of OSA with resistant hypertension among black adults who participated in the Jackson Heart Study (Jackson, MS). OSA was defined according to a respiratory event index > 15/h based on a type 3 apnea screening device. Nearly half of the 664 participants with hypertension (48%) were uncontrolled, and 14% had resistant hypertension. Participants with OSA were two times more likely to have resistant hypertension (OR = 2.0, 95% CI 1.14 to 3.67) following adjustment for demographic and clinical characteristics. Of note, the odds of resistant hypertension were even higher among those with the most severe OSA as defined by a respiratory event index > 30 events/h (OR = 3.50, 95% CI 1.54–7.91). OSA was not associated with uncontrolled hypertension (uncontrolled BP with the use of 1–2 antihypertensive medications). When the percent of time spent in nocturnal hypoxia (oxygen saturation < 90%) was used to define OSA, the pattern of association was similar.

One of the primary innovations of the study by Johnson and colleagues [27••] is that it was conducted exclusively among blacks—the highest risk demographic group for resistant hypertension. The authors hypothesize that persistent disparities in hypertension-related target organ diseases (e.g.,

chronic kidney disease, cerebrovascular disease, heart failure) between blacks and whites [28] could be attributable to OSA or other sleep disorders.

In summary, findings from these two new studies are consistent with prior reports and reviews describing an association of OSA with resistant hypertension in the population.

Clinical Intervention Studies Targeting OSA

Once OSA is identified, it is less clear whether treatment is universally effective for blood pressure lowering. In one meta-analysis of 10 clinical trials [29], the investigators concluded that treating OSA with CPAP has a modest effect on daytime blood pressures that was likely mediated by compliance with CPAP. Treatment was also associated with improvements in nocturnal non-dipping blood pressure patterns observed among patients with OSA [30]. Of note, the authors concluded that the effectiveness of CPAP appeared stronger in participants with the least favorable blood pressure levels at the outset.

In updated meta-analyses in 2016 and 2017, OSA treatment was effective for blood pressure lowering across the BP ranges of hypertension. In a meta-analysis by Liu of 5 RCTs, 24-h ambulatory SBP and DBP were 4.78 mmHg and 2.95 mmHg, respectively, lower ($p < 0.05$) among patients on CPAP as compared with those who were not. Nocturnal DBP was 1.53 mmHg lower among patients on CPAP [31•]. A 2017 review that incorporated an additional RCT yielded similar findings with a similar strength of effect [32•].

In summary, evidence that treating OSA lowers blood pressure is equivocal, though suggestive of effective among those patients who have the poorest blood pressure levels initially. Thus, treating OSA may be a useful adjuvant therapy for adults with resistant hypertension.

Other Domains of Sleep Health and Resistant Hypertension

Prior reports describe an association of other sleep disturbances including sleep restriction, insomnia, and non-restorative (poor quality) sleep, with the prevalence and incidence of hypertension [33, 34]. Disruptions in the body's circadian rhythms, the daily cycle of physical, mental, and behavioral changes that follow a light-dark cycle occur when there is desynchrony between internal circadian rhythms (24-h) and the environment [35, 36]. Circadian disruptions resulting from shift work and/or social factors (i.e., social jet lag) are associated with the onset of multiple metabolic and cardiovascular diseases [37–40]. Each of these sleep disturbances is implicated in the development of hypertension [41–43]. However, there remains a notable paucity of research investigating domains of sleep health other than OSA on blood pressure control among adults with hypertension.

Two pathophysiologic processes highlighted in the prior review as linking OSA with resistant hypertension are endothelial dysfunction and sympathetic nervous system stimulation [22]. These pathophysiologic processes, in addition to inflammation, are observed in the presence of other sleep disturbances including short (< 6 h/night) or long sleep (> 9 h/night), circadian rhythm disorders, and insomnia [44, 45]. In turn, these pathophysiologic processes are associated with hypertension prevalence [46]. Thus, it is biologically plausible that these pathophysiologic processes would continue to contribute to blood pressure control in the setting of hypertension.

It is also plausible that other sleep disturbances are indirectly associated with resistant hypertension through their influence on behaviors. In particular, non-restorative short and poor quality sleep is associated with poorer adherence to recommended lifestyle behaviors related directly to hypertension management and indirectly to weight [47•, 48]. For example, in experimental studies that restrict sleep, adults crave salty and high-fat foods, and observational studies describe less favorable eating patterns (e.g., hypercaloric, low nutrient) among adults with shorter sleep duration [49, 50]. Observational studies report that sleep-deprived individuals are less likely to be physically active [51]. Non-restorative sleep, long sleep, and short sleep are each also associated with higher levels of psychological distress including depression, anxiety, and chronic stress [50, 52••, 53]. Psychological distress may, in turn, be associated with treatment noncompliance in hypertension management. Given the clustering of unhealthy lifestyle behaviors and psychological distress with sleep disturbances, future studies should measure and account for these behaviors.

To date, there is only one published intervention study that targeted habitual sleep using an online sleep intervention containing components of sleep hygiene and cognitive behavior therapy for insomnia. McGrath and colleagues [54] tested the effectiveness of the intervention in participants with self-identified poor sleep and hypertension. The investigators reported improvements in self-reported measures of sleep quality and depressive symptoms; however, they described no difference in 24-h ambulatory SBP between the intervention arm and the vascular health education control arm (difference in mean improvement 0.1 mmHg, 95% CI − 3.4 to 3.2) [54].

It is possible that the effectiveness of sleep interventions may be most pronounced in the highest risk groups with the worst sleep. Disparities in habitual sleep by race/ethnicity have been described [55, 56]. Studies targeting sleep intervention in race/ethnic groups with short duration sleep and poor sleep quality who are at highest risk for hypertension onset and treatment resistant hypertension (e.g., non-Hispanic blacks) may yield different results. Further, studies that apply different intervention strategies (e.g., mindfulness-based

interventions) and that target other domains of sleep health (e.g., insomnia management, circadian disruptions) are warranted.

Sleep and Disparities in Resistant Hypertension

As noted earlier, resistant hypertension is far more common in blacks as compared with non-Hispanic whites [57]. Notable features of the two original studies discussed in the present review is that both included a high proportion of non-white adults or were exclusively comprised of the highest risk group of black adults [26••, 27••]. Consequently, treating OSA and improving sleep quality and duration have the potential to reduce disparities in treatment resistant hypertension between non-whites and whites.

There are established racial/ethnic disparities in other aspects of sleep health (duration, other disorders, and circadian disruptions) [55, 58]. It is plausible that these sleep disturbances mediate the association between race and hypertension management. Prior research supports this hypothesis for prevalent hypertension [59, 60]. It is equally likely, though untested, that these disparities in sleep disturbances may account for some proportion of the disparities in resistant hypertension [42]. Such research is warranted because many of these sleep disturbances are modifiable through behavior change, pharmacotherapies, or psychotherapy. Empirical research on this topic would provide another strategy to enhance efforts to control blood pressure among non-Hispanic blacks and other non-white minorities.

Conclusion

In summary, the relationship of OSA with resistant hypertension is robust across study design, OSA assessment methodology (clinical diagnoses vs. polysomnographic assessment), and population demographics. Further, treating OSA can improve blood pressure control among adults with hypertension at the highest blood pressure levels. Given the high burden of treatment resistant hypertension in non-Hispanic blacks, addressing OSA may be one strategy for reducing racial/ethnic disparities in treatment resistant hypertension. Further research is needed to describe the relationship of other equally important aspects of sleep health, namely habitual sleep duration, common sleep disorders including insomnia, and circadian rhythm disruptions, with treatment resistant hypertension.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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