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REVIEW ARTICLES

Sleep Disordered Breathing and Hypertension

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Abstract: Sleep disordered breathing is frequently associated with repeated arousals and hypoxia resulting from intermittent partial or complete collapse of upper airway during sleep. There is an emerging recognition of the association of this disorder with metabolic abnormalities, coronary artery disease, congestive heart failure and hypertension. Of these conditions, the data associating obstructive sleep apnea and hypertension are the most compelling. This review evaluates the recent literature investigating this association and identifies areas where additional research is needed.

Keywords: Sleep disordered breathing, Obstructive sleep apnea, hypertension, CPAP

Sleep disordered breathing (SDB), including its most severe form, obstructive sleep apnea, is characterized by intermittent partial or complete collapse of upper airway during sleep, frequently resulting in repeated arousals and hypoxia. There is an increasing recognition that SDB is associated with a higher prevalence of cardiovascular disorders including hypertension, coronary artery disease and stroke. Amongst these conditions, the data supporting an association between SDB and hypertension are the most robust. This brief review discusses possible pathophysiologic mechanisms linking SDB to hypertension as well as critically assesses the recent data suggesting a causal relationship.

Pathophysiology

Several possible mechanisms through which SDB may cause hypertension have been proposed. The intermittent narrowing or closure of the upper airway may result in cortical arousals, which, in turn, produces sympathetic activation and leads to an increase in the blood pressure (BP).[1] However, arousals alone may be insufficient to produce sustained hypertension. In the Sleep Heart Health Study, arousal frequency was not an independent factor associated with risk of hypertension.[2] A canine study provides further support for this hypothesis by demonstrating the need for apneas in addition to arousals to induce hypertension.[3] These observations combined with additional data linking intermittent hypoxia in experimental animals to hypertension [4] suggest that hypoxemia, a frequent attendant of respiratory events, may be the sentinel factor producing hypertension in the setting of SDB.

The clinical studies demonstrating increased sympathetic activity from hypoxemia support a causal relationship between SDB-related hypoxemia and daytime hypertension. For example, Leuenberger et al found sustained sympathetic activation and a transient increase in BP in healthy young subjects during voluntary breath holding while breathing hypoxic air.[5] Furthermore, there is a significant correlation between daytime urinary norepinephrine levels and the number of apneas and the severity of nocturnal hypoxia.[6]

Recently, other mechanisms in addition to hypoxemia and enhanced sympathetic activity have also been invoked in the pathogenesis of SDB-related hypertension. An increase in the renin-angiotensin-aldosterone system activity has been observed in the SDB patients, and the activity decreases after treatment with continuous positive airway pressure (CPAP).[7] An impairment of endothelium-dependent vasodilatation may be another potential mechanism underlying the pathogenesis of hypertension in SDB individuals.[8,9,10] SDB may also worsen insulin resistance, which in turn, may be associated with hypertension.[11] Finally, genetic predisposition may influence the presence and the severity of hypertension in patients with SDB.[12]

Epidemiology

A number of large studies provide strong evidence for an association between SDB and hypertension.[2,13-17] Subjects in these studies have included those derived from the community [2,18] as well as those recruited from sleep clinics.[17,19] While most of these studies have been cross-sectional in design, thus precluding determination of causality, Peppard et al employed a longitudinal design and found an association between SDB at baseline and the presence of hypertension four years later in 709 subjects participating in the Wisconsin Sleep Cohort.[18] The association was independent of diverse confounding factors including age, sex, body mass index (BMI), waist and neck circumference, baseline hypertension and weekly cigarette and alcohol use. Furthermore, the odds of developing hypertension became greater as the apnea

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hypopnea index (AHI) increased. These findings are supported by data from the Nurses Health Study in which snoring as a surrogate for SDB was found to increase the risk of incident hypertension over an 8-year follow-up period.[20] Such observations are perhaps the strongest epidemiologic evidence that SDB is a risk factor for the development of hypertension. They are also supported by studies performed in clinical populations. For example, Lavie et al studied sleep apneics who reported using anti-hypertensive medications on a regular basis for more than 6 months and found a higher mean AHI among those whose hypertension had been treated ineffectively (BP >140/90 mm Hg in the morning or in the evening) than among the subjects whose hypertension had been controlled effectively.[21] Similarly, another cross-sectional study revealed a high prevalence of SDB in drug resistant hypertensive patients.[22] A "dose-response" relationship between hypertension and SDB severity has also been demonstrated in a cross-sectional study of 591 patients without a history of systemic hypertension who were referred for a sleep study.[23] In this study, AHI gradually increased with the grade of hypertension: 15.7/hour in normotensive, 18.9/hour in grade 1 hypertension, 27.2/hour in grade 2 hypertension and 30.3/hour in grade 3 hypertension.

Recent studies performed in specific ethnic groups and patients with other medical disorders provide additional evidence linking SDB to hypertension. For example, higher rates of hypertension in SDB patients have been reported among African Americans[24] and nondiabetic dialysis patients.[25] In a related study, Tanigawa et al found a significant association between nocturnal oxygen desaturation and the BP levels in Japanese men in a population-based study.[26]

SDB has been linked to hypertension in children. The Tucson Children's Assessment of Sleep Apnea Study found SDB to be an independent predictor of systolic and diastolic BP elevation in children.[27] Another study also reported greater mean BP variability during wakefulness and sleep in children with SDB.[28] Despite limited data in this age group, the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents recommends obtaining a sleep history in children with hypertension to exclude sleep apnea.[29]

SDB may not only be associated with development of hypertension, it may preclude the normal decline or dipping in BP during sleep. One recent study found a high prevalence of blunted nocturnal dipping in patients with SDB.[30] Notably, non-dipping has been associated with increased cardiovascular morbidity.[31,32]

While the above data suggest a role for SDB in the pathophysiology of hypertension, additional factors need to be considered before adjudging that the relationship between SDB and hypertension has been conclusively established. Some studies have found a correlation between desaturation or movement time, and hypertension rather than the apneas themselves.[33] Likewise, Dhillon et al did not find any difference in the AHI between normotensive and hypertensive SDB subjects, although they did report a decrease in BP with CPAP therapy.[34] Similarly, an earlier population-based study reported no significant increase in the risk of systemic hypertension in patients with sleep apnea.[35] Many studies control for BMI, but not for neck size, which may be another confounder for the association between SDB and hypertension, and may only be partly controlled by adjusting for BMI. Conversely, adjusting for BMI may mask or diminish any relationship between SDB and hypertension if both BMI and SDB are on the same causal pathway for the development of hypertension. Physical inactivity from poor sleep may be an additional factor confounding the relationship between SDB and hypertension. Finally, the possibility of publication bias in favor of positive results suggesting relationship between SDB and hypertension cannot be negated.[36]

Effects of SDB Therapy on Hypertension

The studies observing the effect of SDB treatment on BP constitute another line of evidence supporting a causal role of SDB in the development of hypertension. Recently, a retrospective analysis of hypertensive SDB patients reported a drop in systolic BP by an average of 11.2 mmHg and diastolic BP by 5.9 mmHg with an average CPAP use of 12.1 months.[34] Another study utilizing automated ambulatory 24-h BP monitoring in a prospective manner in 88 consecutive patients found significantly higher mean arterial BP among 62 patients with SDB compared with the remaining 26 with habitual snoring.[37] Of the patients with SDB on CPAP therapy, 52 were followed after 9 months with 24-h BP monitoring. Forty of these patients had a lower BP at follow up than at baseline.

In a prospective study of 11 patients with refractory hypertension (systolic BP > 140 mmHg or diastolic BP > 90 mmHg despite continued treatment with a combination of three or more antihypertensive medications), Logan et al demonstrated a reduction in the daytime, nocturnal and average systolic BP as well as nocturnal diastolic BP with CPAP usage for 2 months.[38] Daytime systolic and diastolic BP fell significantly by an average of 9.3 mmHg and 7.8 mmHg respectively. However, there was no control group. Another prospective randomized trial in 118 patients showed that therapeutic, but not sub-therapeutic, CPAP improved both systolic and diastolic BP during awake and sleep.[39] The benefit was greatest in patients with severe SDB as well as those already being treated with antihypertensive medications. Becker et al. showed a reduction in BP by approximately 10 mmHg, both at night and during the day, after 9 weeks of treatment with therapeutic CPAP in 16 patients.[40] However, subtherapeutic CPAP did not decrease BP despite decreasing AHI by half. Another study assessed changes in BP in 65 patients with SDB after surgery and found a significant correlation between improvement in blood pressure and oxygen desaturation time, but not AHI.[41]

A reduction in sympathetic activity associated with SDB may constitute the physiological basis of the observed attenuation of hypertension with CPAP therapy in these patients.[42,43] An improvement in autonomic nervous system dysfunction in patients with SDB with medical or surgical therapy has also been demonstrated in some studies.[44,45]

However, not all studies support an association between SDB and hypertension. In contrast to the evidence cited above, a study comparing patients on CPAP therapy for SDB and those discontinuing CPAP therapy found no significant differences in the incidence of hypertension over an average of 7.5 years of follow-up.[46] Dimsdale et al. randomized 39 SDB patients with AHI > 20, with or without hypertension, to receive therapeutic or placebo CPAP (pressure 2 cm H_2O) for 1 week. There was an equivalent decrease in daytime BP in both therapeutic and sub-therapeutic CPAP treatment groups suggesting a placebo effect.[47] This study , however, was limited by absence of data beyond 1 week of CPAP use. Another study by Hermida et al. did find a high prevalence of hypertension (77%) among 122 patients with SDB but did not show any significant effect of 4 months of CPAP use on BP in the

83 patients who accepted this therapy.[48] In another randomized, placebo-controlled, cross over study of 68 normotensive patients, Faccenda et al. compared the change in BP with CPAP therapy and oral placebo for 4 weeks and found only a minimal difference with CPAP therapy.[49] However, CPAP did reduce diastolic BP by 5 mmHg in patients with at least a 4% oxygen desaturation occurring more than 20 times per hour. Yet another study assessed the effects of CPAP on 55 patients with severe SDB (AHI $\geq$ 30) without daytime sleepiness.[50] Subjects were randomized to receive therapeutic (n = 29) or sham (n = 25) CPAP for 6 weeks. The use of therapeutic CPAP did not augur an improvement in BP or improved BP regulation in nondippers (12 in each group). Notably, the average BP in these subjects was in the normal range. In a study which randomized 55 patients with CHF and SDB to 3 months of CPAP or control, there were no significant changes in systemic blood pressure although CPAP resulted in an improvement in the left ventricular heart function.[51] This is in contrast to an earlier study which reported reduction of the daytime systolic BP from a mean of 126 mm Hg to 116 mm Hg in 12 patients with a depressed left ventricular ejection fraction after CPAP use for 1 month, compared to no significant change in the control group.[52]

Although the results of treatment trials have not universally favored a beneficial effect of CPAP on hypertension, it does appear that a large number do support a causal relationship. Differences in study designs and populations may explain some of the heterogeneity in results.

Conclusions and Future Directions

Recent epidemiologic studies provide compelling evidence for an association between SDB and hypertension. However, additional data from longitudinal studies will be needed to confirm whether there is an increased incidence of hypertension in persons with SDB. Results from the Sleep Heart Health Study may provide such information. Future studies also need to be more rigorous in controlling for confounding factors. A standard definition of SDB will also help in making meaningful deductions from these studies. Furthermore, the mechanistic link between SDB and hypertension needs to be better elucidated. The availability of vascular pathology data will also help define the vascular consequences of the presence of SDB.

Larger, better designed studies are also needed to understand the antihypertensive effects of CPAP. Whether CPAP has an equivalent BP-lowering effect in all subgroups, or the efficacy is predominantly seen in particular racial, gender or age groups, needs to be elucidated. Many trials evaluating effect of SDB therapy and changes in BP are limited by methodological shortcomings. Lack of proper randomization, inadequate blinding and inclusion of both normotensive and hypertensive patients are some of the concerns in previous studies. Comparison of results among studies is further hampered by the lack of a common definition of apneas and hypopneas (amplitude of decrease in signal, requirement of desaturations, arousals etc.) and different definitions of hypertension. The end points (decrease in BP by a specific percentage or normalization of BP) need to be better defined. Finally, current research does not reveal whether the purported anti-hypertensive benefits of CPAP can be achieved in most patients by medications alone.

In conclusion, data suggesting an association between SDB and hypertension has accumulated over the years and recent studies provide evidence for a causal relationship. Nevertheless, additional larger and methodologically sound longitudinal and interventional studies are needed to confirm the causal nature of the association. In the meantime, it is recommended that a thorough sleep history to look for SDB be regularly obtained in patients with severe refractory hypertension with no obvious etiology. The treatment should include therapy for SDB as well as that for hypertension.

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