Invited review

Hypertension and obstructive sleep apnoea

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Abstract

Several epidemiological and experimental studies have demonstrated a close relationship between sleep-disordered breathing and cardiovascular disease. Obstructive sleep apnoea has been linked to hypertension in a dose-dependant and time-related manner. Postulated underlying mechanisms involve autonomic nervous system alterations, chemoreceptor and baroreceptor responsiveness impairment, higher levels of vasoactive hormones and impaired endothelial function. Continuous positive airway pressure (CPAP) therapy for obstructive sleep apnoea may significantly improve blood pressure control and influence target organ damage, previously ascribed to hypertension alone.

Key words: obstructive sleep apnoea, hypertension, continuous positive airway pressure therapy.

Introduction

Physiological sleep plays a significant role in cardiovascular control. Cyclical sleep stages coincide with related cardiovascular variations. Blood pressure declines to the lowest values during sleep stages N3, rising again in the rapid eye movement (REM) stage. Overall blood pressure load during sleep decreases at least 10% as compared to the waking state in healthy humans. Sleep deprivation and shorter sleep time itself result in higher blood pressure and an increased risk for hypertension [1, 2]. Recurrent apnoeic episodes, a condition commonly known as sleep apnoea, provokes a lot more detrimental stimuli beyond mere sleep architecture disruption. Cessation of breathing naturally results in periods of hypoxia and hypercapnia, rapid and sustained autonomic system activity changes, and pleural pressure swings. All of these, paralleled by sequent metabolic, hormonal, and rheological alterations, add risk to the incidence of arterial hypertension, as well as early target organ damage. Experimental and epidemiological studies have shown sleep apnoea to be an independent risk factor and prognostic indicator for ischaemic heart disease, arrhythmias, and stroke.

This paper discusses obstructive sleep apnoea and its link to systemic hypertension.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is characterized by recurrent periods of breathing cessations during sleep caused by complete or partial upper

airway collapse. Obstructive sleep apnoea has an estimated prevalence of 9 to 24% in middle-aged working women and men, respectively [3]. Attended polysomnography (PSG) has been confirmed to be a diagnostic tool for any type of sleep-disordered breathing. Simultaneous recording of electrophysiological signals allows the scoring of sleep stages as well as describing breathing events. The arbitrary cut-off value used for the distinction between physiology and disease for sleep apnoea has been set at 5 events per hour of sleep (apnoea hypopnoea index – AHI). Disease has been further classified as mild sleep apnoea (AHI 5-14.9), moderate (AHI 15-29.9) and severe (≥30 events per hour of sleep). Sleep apnoea syndrome refers to relevant PSG findings coinciding with disease symptoms, e.g. excessive daytime sleepiness, unrefreshing sleep, choking sensations during sleep, recurrent awakenings from sleep, daytime fatigue and impaired concentration [4]. Since PSG recordings are time- and money-consuming, it is also acceptable to apply polygraphic tests (no EEG, EOG, EMG) to subjects highly suspected of having OSA, both to rule in and rule out the disease. This strategy requires available pre-tests that increase the likelihood of OSA (patient's medical history, information from a sleep-partner questionnaire) [5]. Of widely-used forms, the Berlin questionnaire (BQ) has been confirmed to be a sufficient tool to divide patients into high and low OSA probability subgroups. The BQ has been validated in primary care patients as well as atrial fibrillation patients [6, 7]. The BQ has not been proven a valuable tool for referrals to the sleep laboratory [8] (see appendix for the instructions for this tool).

Evidence of associations between obstructive sleep apnoea and arterial hypertension

A number of research studies have evidenced a link between obstructive sleep apnoea and abnormal blood pressure control. Animal experiments have revealed mimicked apnoeas to be a cause of elevated systemic blood pressure and development of hypertension [9]. In cross-sectional studies OSA patients demonstrate increased blood pressure and a higher incidence of hypertension as compared to controls [10-12]. On the other hand, breathing disorders during sleep are more prevalent in patients with arterial hypertension, particularly if refractory to conventional drug therapy [13-15]. Up to 83-85% of hypertensive individuals with 3 or more blood-lowering medicines may have previously undiagnosed obstructive sleep apnoea. Compelling data indicating a causative role of sleep apnoea in the pathogenesis of hypertension in humans derives from the Wisconsin Sleep Cohort Study [16]. Data analysis provided evidence of a dose-response relationship between severity of sleep-disordered breathing represented by AHI, and the odds for hypertension in a prospective four-year observation. The study was conducted among working adults and was controlled for such confounders as baseline hypertension status, BMI, neck and waist circumference, age, sex, and weekly use of stimulants. The OR for the incidence of hypertension were 2.03 with an apnoea-hypopnoea index of 5.0 to 14.9 events per hour as compared to none, and 2.89 for moderate-to-severe disease. It is worth mentioning that even a few apnoeas per hour of sleep, regarded to be within normal limits (AHI<5), conferred a risk of hypertension (OR 1.42). The strength of this association is attenuated by aging [17]. Analysis of data from a multicentre project, the Sleep Heart Health Study, has shown an independent association of OSA and hypertension, but only in a group of middle-aged subjects, whereas no such correlation was found in individuals aged over 60. Further analysis of SHHS data revealed that self-reported excessive daytime sleepiness may considerably modify risk for hypertension. Marked sleepiness strengthens the association between AHI and odds for hypertension [18]. Those findings remain consistent with results from interventional studies [19].

Since early haemodynamic alterations secondary to recurrent apnoeas are generally detectable during the night, OSA patients may not exhibit daytime hypertension [20]. It has been estimated that up to 30% of newly diagnosed OSA patients may have nighttime hypertension [21]. Furthermore, prospective observation of the Wisconsin Cohort revealed worsening of blood pressure profile in sleep apnoeic patients over time [22]. This underscores the need for ambulatory blood pressure evaluation in this group of patients [23].

Alarming signals come from studies on children whose early-age hypertension may significantly precipitate target organ damage. Although data are inconsistent and no referral scores for apnoeic events are available for children, the weight of evidence suggests obstructive sleep apnoea to be involved in excessive blood pressure load and increased risk for hypertension in youths [24-26].

Target organ damage

Obstructive sleep apnoea confers the risk of target organ damage primarily ascribed to hypertension itself. Animal and human studies suggest impaired left ventricular function and structure resulting from recurrent apnoeas [27-33]. Research testing correlations between sleep apnoea and ischaemic heart disease confirm a close relationship of those two conditions. Positive associations have been found between the incidence of ischaemic heart disease among sleep apnoea patients as well as heart disease prognosis

with respect to OSA severity [34-39]. Another detrimental effect of obstructive sleep apnoea on cardiac function concerns heart rhythm control. Several observational studies have shown that OSA increases the prevalence and reoccurrence of cardiac arrhythmias [40-43]. Neurological studies have also demonstrated a link between sleep-disordered breathing and cerebrovascular disease [44]. Obstructive sleep apnoea patients are at an increased risk for both a first-time cerebrovascular event as well as a subsequently worse stroke prognosis. The latter appears to be positively influenced by continuous positive airway pressure (CPAP) therapy [45-47].

Mechanisms linking sleep apnoea to hypertension

Autonomic nervous system

Oxygen and carbon dioxide fluctuations resulting from recurrent apnoeas overstimulate the autonomic nervous system via chemoreceptors. Both sympathetic and parasympathetic activity rise progressively during the time of apnoea to be eventually enhanced by arousal. In that time increased sympathetic neural tone promotes peripheral vascular resistance, whereas heart action chiefly depends on parasympathetic overactivity [48]. The resumption of breathing coincides with constricted peripheral vasculature and rapid acceleration of heart rate, which in turn provokes a steep rise of arterial blood pressure. Apnoea termination has been evidenced to accompany systolic readings as high as 250 mm Hg, which may be true even in those individuals whose daytime resting blood pressure shows no pathology. Human observational studies using different investigative tools have also revealed higher levels of daytime sympathetic nerve activity in OSA patients [48-51]. Among the underlying recognized mechanisms responsible for increased sympathetic activity during the waking state, chemoreceptor dysfunction and impaired baroreceptor responsiveness may play a significant role [52-54]. Supportive information for this hypothesis comes from interventional studies. Introduction of CPAP therapy has been followed by marked and sustained reduction in the sympathetic drive measured both by plasma and urinary norepinephrine concentrations as well as microneurography [55, 56]. High levels of sympathetic activity are paralleled by impaired cardiovascular variability during the waking state. This alteration is marked even in OSA patients without diagnosed hypertension or heart failure. Sleep apnoeics exhibit marked increase in blood pressure variability, faster heart rate and decreased RR variability [57]. The measure of this derangement is closely linked to the disease severity. Both sympathetic overactivation and abnormal cardiovascular variability in sleep apnoea patients may contribute to the increased risk of future hypertension [58] as well as target organ damage [59].

Aldosterone

The interaction between obesity, sleep apnoea and aldosterone is vaguely elucidated. It has been suggested that the visceral adipose measure correlates with plasma aldosterone levels [60]. At the same time obesity plays a key role in sleep apnoea pathogenesis. Previous studies suggesting higher levels of plasma aldosterone and aldosterone urine excretion in OSA patients were not BMI-controlled [61, 62]. Such a correlation in a dose-response manner has been found in a fully-controlled model in subjects with resistant hypertension [63]. The authors of this paper hypothesize that hyperaldosteronism through water retention confers the risk of higher AHI. A contrasting approach to this problem involves studies testing an inverse association. Assuming that recurrent sleep apnoeic episodes lead to a secondary increase in concentrations of plasma aldosterone, treatment with CPAP would promote a decline in hormone levels. The results of such short- or long-term observations remain very inconsistent [62-66].

Endothelin-1

Animal studies investigating the influence of either sleep deprivation or intermittent hypoxia (conditions linked to apnoeas) on endothelin-1 (ET-1) concentrations have revealed an excessive release of this potent vasoconstrictor [67, 68]. However, comparative and interventional studies in OSA patients have brought conflicting results [69-72]. One possible explanation for these discrepancies might be the different methodologies used in these studies. Another study testing a circulating precursor of ET-1 (characterized by significantly longer half-life) supports the hypothesis of impaired hormone homeostasis further reversible by CPAP [73].

Nitric oxide

It has been evidenced that OSA patients demonstrate impaired endothelium-dependent vasodilation [74, 75]. Experiments with acetylcholine (ACH stimulates NO-mediated vasodilation) and nitroprusside (a direct donor of nitric oxide) revealed a diverse vascular response in OSA patients. The administration of a direct donor of nitric oxide results in vascular dilation comparable to controls, whereas stimulated endogenous NO release is attenuated [76]. One possible explanation for this phenomenon would be an increase in asymmetric dimethylarginine (ADMA), an endothelial nitric oxide

synthase antagonist. Administration of CPAP therapy results in a decrease in ADMA levels which coincides with improvement in NO-dependent vasodilation [77].

Continuous positive airway pressure therapy

The effect of CPAP therapy on blood pressure control varies in different sleep apnoeic populations. The weight of evidence generally favours hypotensive action of CPAP in OSA patients. The first night with applied positive pressure results in an acute and clear-cut reduction in post-apnoeic blood pressure surges [78]. Although short-term observations are inconsistent, patients' follow-ups reveal a statistically significant reduction in systolic and diastolic blood pressure [79-81]. Once OSA management has been started, an effort guaranteeing that no residual apnoeas are left has to be made. Interventional studies have shown no benefit in blood pressure control with subtherapeutic CPAP [82, 83]. It is also assumed that cardiovascular response to CPAP treatment varies in regard to sleep apnoea severity, initial blood pressure readings, and quantitative antihypertensive treatment [84]. Patients with advanced sleep-disordered breathing appear to receive major hypotensive benefit from CPAP therapy when compared to controls. Long-term follow-ups of subjects using CPAP devices suggest a time-related improvement in blood pressure control [85]. Another aspect of continuous positive pressure therapy is its relation to circadian blood pressure pattern. Sleep apnoea might be responsible for the previously described insufficient nocturnal decline of BP or even the increase of systemic blood pressure during the night. It has been demonstrated that CPAP therapy may at least partially overturn this detrimental condition [86]. So far, no proven hypotensive action of CPAP has been evidenced in normotensives [87] as well as hypertensive OSA patients without concomitant excessive daytime sleepiness [88]. The latter data emphasize the importance of physiological sleep architecture in cardiovascular control. Beside several demonstrated benefits for patients on CPAP therapy, adherence to this procedure remains at a poor level [89].

Conclusion

There is growing evidence of a causal and dose-dependant relationship between obstructive sleep apnoea and hypertension. Unmanaged OSA may also be implicated in a higher risk for target organ damage previously ascribed to hypertension alone. Long-term CPAP treatment attenuates neural and hormonal abnormalities relevant to circulatory control, which translates into a decrease in blood pressure load and an improved overall prognosis.

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APPENDIX

The Berlin Questionnaire (BQ)

High risk of OSA is determined by positive responses to at least 2 of the following 3 criteria:

1) symptoms at least 3 times per week for at least 2 snoring questions,
2) somnolence during daytime and/or while driving at least 3 times per week,
3) history of hypertension or BMI>30 kg/m^2.

Additional information needed to be saved (gender, age, weight, height, neck circumference)

1. Has your weight changed in the last 5 years?
   - ☐ increased
   - ☐ decreased
   - ☐ no change

2. Do you snore?
   - ☒ yes
   - ☐ no
   - ☐ don't know

If you snore:

3. Your snoring is
   - ☐ as loud as breathing
   - ☐ as loud as talking
   - ☐ louder than talking
   - ☒ very loud

4. How often do you snore?
   - ☒ nearly every day
   - ☒ 3-4 times a week
   - ☐ 1-2 times a week
   - ☐ 1-2 times a month
   - ☐ never or nearly never

5. Does your snoring bother other people?
   - ☒ Yes
   - ☐ No

6. Has anyone noticed that you quit breathing during your sleep?
   - ☒ nearly every day
   - ☒ 3-4 times a week
   - ☐ 1-2 times a week
   - ☐ 1-2 times a month
   - ☐ never or nearly never

7. How often do you feel tired or fatigued after your sleep?
   - ☒ nearly every day
   - ☒ 3-4 times a week
   - ☐ 1-2 times a week
   - ☐ 1-2 times a month
   - ☐ never or nearly never

8. During your waking hours, do you feel tired or fatigued?
   - ☒ nearly every day
   - ☒ 3-4 times a week
   - ☐ 1-2 times a week
   - ☐ 1-2 times a month
   - ☐ never or nearly never

9. Have you ever nodded off or fallen asleep while driving a vehicle?
   - ☒ yes
   - ☐ no

10. Do you have high blood pressure?
   - ☒ yes
   - ☐ no
   - ☐ don't know