Personal Opinion

Sleep-related breathing disturbances: their pathogenesis and potential interest to the nephrologist

Donald S. Silverberg, Adrian Iaina and Arie Ocksenberg

Department of Nephrology, Tel Aviv Medical Center, Weizman 6, Tel Aviv and 1Sleep Disorders Unit, Loewenstein Rehabilitation Hospital, Raanana, Israel

Introduction

Simple snoring and obstructive sleep apnea (OSA) are both common sleep-related breathing disturbances and are characterized by recurrent upper airway obstruction of different degrees of severity during sleep. There is growing evidence that both of these conditions play an important role in the production of essential hypertension (EH) and secondary hypertension, including the hypertension of chronic renal failure (CRF) [1,2]. In CRF, OSA may be an important contributor to the production of daytime and nocturnal hypertension, and to the progression of the renal disease. OSA may also play a significant role in the increased incidence of cardiovascular complications seen in CRF. In addition many symptoms in CRF which have been blamed on uremia could actually be due to the sleep-related breathing disturbances [1,2].

Sleep-related breathing disturbances and essential hypertension

About 80% of people with EH are habitual snorers, i.e. they snore every night or almost every night [2–4]. About half of these snoring EH patients (i.e. ~40% of all those with EH) have OSA (defined as five or more apneic and hypopneic events per hour of sleep) [2–4]. What is the evidence that the OSA alone or habitual snoring without OSA could actually cause essential hypertension?

Similarities between OSA and EH

There are an enormous number of similarities between EH and OSA. Both are more common in habitual snorers than in non-snorers, in the obese than in the non-obese, in young and middle-aged men than women, in older compared to younger women, and in African Americans compared to white Americans. In both conditions there is an increased prevalence of cardiovascular events, renal pathology, failure of the blood pressure to fall normally during sleep, glucose intolerance and insulin resistance, exaggerated pressor and ventilatory responses to hypoxia, exaggerated pressor responses to mental stress, reduced baroreceptor sensitivity, abnormal cognitive function, impotence and headaches [2].

The failure of antihypertensive medications to reduce coronary heart disease morbidity and mortality in EH as much as would be expected by epidemiological studies [5,6] could be in part due to the fact that the associated sleep-related breathing disturbance was not treated. The relatively high rate of occurrence of myocardial infarction [7] and stroke [8] during sleep and during the early waking hours could be, in part, to the sleep-related breathing disturbance with its associated hypertension, hypoxia and increased platelet activation and aggregation. Other common findings in EH and OSA include increased hematocrit levels, hyperuricemia, reduced renin levels during sleep, increased sympathetic activity, elevated atrial natriuretic factor, elevated ratios of vasoconstrictor to vasodilator prostaglandins, reduced testosterone levels in men, reduced endothelium derived relaxation factor, increased blood viscosity, increased fibrinogen levels, reduced blood fibrinolytic activity and increased platelet activation and aggregation [2]. The pattern of inheritance of OSA and EH is also similar [2]. If OSA and habitual snoring are indeed important causes of EH, it is possible that the crucial characteristics that are inherited in these conditions are the abnormal bony and soft tissue structures in the pharynx that result in a smaller than normal posterior airway space and therefore cause an increased tendency to upper airway obstruction and increased upper airway resistance during sleep.

Epidemiological and intervention studies relating OSA to hypertension

The prevalence of EH is much higher in OSA patients (using the above criterion of sleep apnea) than it is in the general population (50% vs. 20%) [1–4]. Conversely the prevalence of OSA is much higher in
The evidence that snoring even without OSA can cause EH?

The prevalence of EH is, on the average, two to three times higher in snorers than in non-snorers [10,11]. Conversely, the prevalence of snoring is, on the average, two to three times higher in EH than it is in normotensives [10,11]. Even when the confounding variables mentioned above such as age, sex and obesity are taken into consideration many, (but not all), epidemiological studies have found that snoring is still an independent risk factor for hypertension [10,11]. One major problem with snoring studies is that they often do not differentiate OSA patients (the vast majority of whom are habitual snorers [3]) from habitual snorers without OSA (non-apneic snorers). However, when they do, these non apneic habitual snorers have also been found in some studies to have about twice the prevalence of EH as normal non snorers [4]. Indeed in some studies the prevalence of EH in these non apneic habitual snorers has been found to be similar to that of OSA patients [12,13]. Of particular significance is the fact that treatment of these non apneic snorers with nasal continuous positive airway pressure (nCPAP) has reduced their 24 h ambulatory blood pressure [14].

The blood pressure during sleep in EH and OSA

About one-third of all EH patients [15], as many OSA patients [1,2], fail to reduce their mean BP during sleep by at least 10% compared to the mean BP during waking hours. These EH patients, so-called non dippers, have been found to have a high prevalence of habitual snoring and OSA [16], and an increased number of short arousals [17] during sleep. These arousals are probably due to periods of partial airway obstruction during sleep which result in increased work of breathing, and they are associated with bursts of increased sympathetic activity and increased BP. Thus the non dipping so often seen in EH may well be due to these sleep disturbances. In a recent study it was found that the more short arousals there were during sleep in non-apneic snorers, the greater was the chance that they had EH [18].

OSA and renal disease

The high prevalence of OSA seen in CRF [19,20] has been blamed on the uraemia itself [19], but dialysis does not improve the sleep disturbance [21]. Could not, therefore, the opposite be the case? Could it be that the physiological changes caused by OSA contribute to progression of renal disease? Proteinuria, for example, is often seen in OSA [22–24], and successful treatment of the OSA patients has resulted in reduced protein excretion [24–26], suggesting that OSA itself is damaging the kidney. In one study, the renal biopsy in a patient with OSA revealed changes of focal glomerulosclerosis [27], the lesion frequently associated with progressive deterioration in renal function. The rate of progression of CRF is greater in non-dippers than in dippers [28], and, as mentioned previously, non-dipping is seen frequently in OSA [1,2] and in CRF [29]. It is possible, therefore, that in many cases of CRF it is the OSA itself that causes the lack of nocturnal dipping of BP as well as the daytime hypertension, and that these, combined with the frequent episodes of hypoxia and hypercapnia that occur during the frequent sleep apneic events, all contribute to the progression of the renal disease. In addition, common ‘uraemic’ symptoms such as tiredness, excessive daytime sleepiness, restless sleeping and reduced cognitive function could be due, in many instances, to the associated OSA, since these types of symptoms often improve after its successful therapy in uremic patients with OSA [30]. In eight non apneic dialysis patients who were heavy snorers, we found that having them sleep with a nasal dilator device (Breathe Right Nasal Strips) that reduces nasal resistance during sleep by at least 10% compared to the meanBP during waking hours, and/or 24 h BP was seen. In addition in 10 of 12 of these studies, when the BP was measured at night, it was found to fall significantly [1,2]. Conversely, in patients with OSA who were already successfully treated for this condition, the BP rose when the treatment was stopped, only to fall rapidly again when treatment was restarted (9).

The high prevalence of coronary heart disease, stroke and congestive heart failure (CHF) seen in CRF could be at least partially explained by the associated OSA since it is known that these complications are extremely common in OSA as well [1,2]. Dialysis patients with OSA have higher 24 h BP levels [32], higher nocturnal BP [33], and more target organ damage (greater left ventricular hypertrophy and end diastolic diameter) [33] than those without OSA. This is not just of theoretical interest, since, in OSA, angina pectoris, cardiac arrhythmias, and CHF can be improved by successful treatment of OSA [1,2]. Successful treatment of OSA in CRF might therefore reduce the high
cardiovascular morbidity and mortality seen in this condition.

OSA can cause renal symptoms even in people with normal renal function, including nocturnal polyuria, nocturia and enuresis [1,2].

Other types of secondary hypertension

In diabetes, hypothyroidism, acromegaly and excessive alcohol intake there is an increased prevalence of OSA [2]. Insulin resistance in diabetics with OSA can be improved by treating the sleep-related breathing disturbance, suggesting that OSA may play a role in its production, possibly because OSA increases sympathetic activity which may increase insulin resistance [2]. Treatment of patients with hypothyroidism and acromegaly often improves both their associated OSA and HT, suggesting that the increased prevalence of HT in these conditions may be related to the OSA. Ingestion of alcohol can cause or worsen OSA, and excessive alcohol intake can also cause HT. The improvement of HT after abstention from alcohol, therefore, could be explained by the improvement in the sleep disorder.

Possible pathogenetic mechanisms for the hypertension in OSA and habitual snorers

The mechanisms whereby partial or complete airway collapse during sleep causes hypertension are still unclear [1,2]. In OSA the frequent apneic events are associated with intermittent episodes of hypoxia, hypercapnia, and increased effort of breathing. All these factors, together or separately, can cause frequent arousals during sleep and all four of these factors can cause frequent bursts of sympathetic activity and consequently an increase in systemic as well as pulmonary blood pressure. Chronic exposure of the blood vessels to the increased sympathetic activity and hypertension may cause vascular alterations that lead to persistent hypertension and organ damage. Other changes that may also result from the sleep disturbances and contribute to making the HT persistent throughout the day and night include reduced baroreceptor sensitivity (perhaps caused by the effect of hypoxia on the baroreceptor), an increased ratio of vasoconstrictor to vasodilator prostaglandin production, increased endothelin production, reduced endothelium derived relaxation factor, polycythemia (which often occurs in OSA), increased intracranial pressure, and renal damage [1,2].

Treatment of OSA and snoring

Excellent reviews have recently been published on the treatment of OSA [34] and snoring [11] and this will not be discussed here.

Diagnosis of OSA

This subject has been reviewed recently [35]. The two most important questions that physicians should ask hypertensive patients in order to detect OSA or habitual snoring are ‘Do you snore?’ and ‘Do you doze off or fall asleep easily during different passive activities such as sitting and reading, watching TV, sitting inactive in a public place (such as a theater or movie), sitting as a passenger in a car, sitting and talking to someone and, most important of all, while driving a car?’. Questioning the patient’s spouse or roommate about whether the patient suffers from the above symptoms, especially apneic episodes, may also be useful and might even give information that is a great deal more accurate than what the patient reports. The most common physical findings in OSA are obesity, especially abdominal obesity, and an increased neck circumference.

Patients who have a positive history of sleep related breathing disturbances or suggestive physical findings should be sent to a Sleep Disorders Unit for an overnight polysomnography study which is currently the gold standard for an objective and accurate diagnosis of the presence and severity of OSA.

Summary

For about 120 years we have been looking for the ‘cause’ of essential hypertension [36]. It is possible that we have merely been wandering through its graveyard, looking at the pathogenetic mechanisms but never the actual cause? Here we pass the gravestone of increased sympathetic activity; there the gravestone of low renin activity. Here high endothelin; there low EDRF. Here high thromboxane A2; there low prostacyclin. It is possible that all these and so many other pathogenetic factors are all due to one basic defect? Is it possible that, in the dead of night while patients with EH have been sleeping, the villain has been lurking in their mouths, stuck somewhere at the back of their throats, hidden from view yet choking them hundreds of times a night. But this intermittent strangulation has not occurred silently. On the contrary, it has made its presence felt in the most irritating way, with snores, groans, grunts, gasps and frightening periods of total apnea. But we, their physicians, never asked about these symptoms, or, if we did, we never paid heed to them. This is clear from the fact that, most cases of OSA occur in association with EH yet are not diagnosed [37]. Perhaps the next ‘arousal response’ should be the arousal of physicians’ consciousness so that they can at long last wake up to the existence of the close connection between sleep-related breathing disorders and hypertension and breathe some new life into the treatment of two old diseases—essential hypertension and secondary hypertension. Early diagnosis and treatment of the sleep-related breathing disorders may not only make the patient feel much better, (something our antihypertensive
medications do not always do), but may reduce the blood pressure and prevent the progression of renal and cardiovascular damage as well.

References

37. Dement WC, Mitler MM. It’s time to wake up to the importance of sleep disorders. JAMA 1993; 269: 1548–1550.