

Sleep apnoea and snoring: potential links with vascular disease

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Snoring and sleep apnoea are now widely recognised medical and public health problems.¹ While the mechanisms and immediate effects of sleep disordered breathing (SDB) on the sufferer are beginning to be better understood, the full extent of the problem and its potential links with other common disorders is less well known.

There are now a number of epidemiological studies indicating that sleep apnoea is a common disorder.²⁻⁷ Also emerging from these varied studies is a picture in which snoring and sleep apnoea appear to be linked to the common vascular diseases. This association, however, is not universally accepted. One view held by some commentators in this field questions the presence of any such link; instead it is proposed that any relative increase in cardiovascular disease among patients with sleep apnoea reflects an overlap of certain common risk factors, such as obesity, within the patient population.

The broad question which this symposium proposes to discuss is what links, if any, exist between snoring, sleep apnoea and vascular disease, with a particular emphasis on the potential associations with heart disease. Furthermore, the strength of these scientific and epidemiological associations will be considered. The purpose of this brief review is to set the background against which the other contributions to this symposium are made.

Snoring and sleep apnoea: Pathophysiology

Whatever controversy there may be about the significance of snoring and sleep apnoea, there remains little doubt that both conditions are extremely common. The first large scale epidemiological study that looked at the prevalence of snoring was that of Lugaresi *et al*⁸ in which a questionnaire was used to estimate the prevalence of snoring in a population of 2858 people in San Marino in Italy. About 24% of men and 14% of the women included in this study were reported to snore habitually. Several subsequent studies, again using a questionnaire approach, proceeded to estimate the differences in the prevalence of snoring between women and men and across age groups.⁹⁻¹⁴ Reported snoring was indeed common in both sexes and could be found in all ages—most commonly in middle aged men in whom estimates of habitual or frequent snoring ranged from 9% to 20%—but snoring was by no means confined to this group. Furthermore, this early work established that snoring was indeed related to symptoms such as daytime sleepiness, sleep difficulty, and irregularities of the sleep/wake schedule.

Around the time of these early questionnaire surveys, other work had begun to establish the strong link between heavy habitual snoring and obstructive sleep apnoea. The development of a number of different portable sleep monitoring devices provided a means by which population based surveys could be combined with overnight recording and measurement of breathing during sleep to estimate better the prevalence of SDB. In one such study of 294 healthy middle aged men living in the Western Australian rural community of Busselton we estimated the prevalence of sleep apnoea (respiratory disturbance index >10 events/hour) to be 10%.¹⁵ The earlier data from the Wisconsin Sleep Cohort Study provided an estimate of similar magnitude.³ One simple but very important fact which both of these studies revealed is that the prevalence of disturbed breathing in sleep and the prevalence of the “syndrome”—the combination of both sleep apnoea and daytime symptoms such as excessive daytime sleepiness attributable to sleep disordered breathing—are very different. For example, in our study, while 10% of men aged 40–65 years had an apnoea/hypopnoea index of 10 or more, only half this number complained of excessive daytime sleepiness. This raises the question of the significance of 10 apnoeic events per hour in sleep without any evidence of daytime sleepiness. Is the possible link between apnoea and vascular disease related to the number of apnoeic events per se? If so, are we facing the prospect of treating otherwise asymptomatic apnoea as a preventative measure in the same way that we treat the typically asymptomatic patient with systemic hypertension?

The other very important fact that emerges from these epidemiological studies is that, in any sample of people, a very high proportion will report symptomatic excessive daytime sleepiness; this will be reported in the absence of any other history of snoring and sleep apnoea. In other words, excessive daytime sleepiness is a very common complaint which in its own right does not necessarily translate into a diagnosis of sleep apnoea. This background is important to keep in mind when we discuss the well known symptoms and signs of sleep apnoea.

The syndromes

The commonest disorder of breathing during sleep is snoring, but in its own right this condition is neither a syndrome nor a disease. However, in some circumstances, heavy obstructed snoring may indeed be associated with a range of daytime awake deficits and may be regarded as a medical problem rather than simply a

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social nuisance. Importantly, it is not known if heavy snoring alone is the key factor in the emerging reports of a link between SDB and vascular disease. There is no reason to assume that any potential link between SDB and cardiovascular disease must relate purely to obstructive sleep apnoea, even though most researchers in this field will immediately think of the many pathophysiological consequences of the typical apnoeic cycle.

The commonest and best known sleep linked breathing disorder is the obstructive sleep apnoea syndrome. In this syndrome there is not only repetitive upper airway obstruction during sleep, during which the subject continues to make efforts against a closed upper airway, but this disordered breathing during sleep is accompanied by an array of daytime symptoms dominated by excessive daytime sleepiness. It is this syndrome—now widely recognised and understood—that will be the focus of much of this symposium.

In fully considering the spectrum of SDB, however, mention should be made of a relatively newly recognised syndrome referred to as the “upper airway resistance syndrome”.¹⁶ It is clearly a variant of obstructive sleep apnoea. These subjects have daytime sleepiness but do not have the typical sleep study recording of repetitive obstructive apnoeic events. While they may snore heavily, more often these patients make little in the way of any audible sound when breathing during sleep. If measured, large swings in intrapleural pressure may be demonstrated to accompany each partially obstructed inspiratory effort, indicating a high level of effort against a very narrowed or almost closed upper airway. The most convincing evidence of the existence of this syndrome comes from the effectiveness of nasal continuous positive airway pressure (CPAP) in its treatment. Nasal CPAP reduces the resistance to breathing in the upper airway, lessening the intrapleural pressure swings with each breath. The most noticeable subsequent benefit to the patient is a marked reduction in daytime sleepiness that can be quantified by a significant improvement in tests of daytime sleepiness such as the multiple sleep latency test. Importantly, this variant also makes the point that the absence of daytime sleepiness and snoring does not necessarily exclude sleep apnoea as a clinical condition.

The most important issue which arises from what appears to be variants of the condition we call sleep apnoea is that we still do not know precisely which elements of the pathophysiology lead to which symptoms or pathological consequences. The abnormal breathing characterised by the onset of upper airway obstruction followed by no airflow, despite increasingly powerful efforts to breathe against the closed upper airway, and then a transient arousal from sleep which leads to a return of upper airway muscle tone and relief (albeit transient) of the upper airway obstruction are all obvious and impressive events to anyone who observes such a patient during sleep. The core pathophysiological events that are widely considered to lead to the many symptoms and signs are the

repetitive asphyxia (fall in oxygen and rise in carbon dioxide) and the repetitive arousals, relentlessly fragmenting and destroying sleep structure. There is little doubt that these two key consequences of the upper airway obstruction in sleep do indeed operate in fully developed sleep apnoea, and produce many of the symptoms and pathological consequences. However, the mistake may be to assume that these are the only two mechanisms. Although there is no doubt that the repetitive arousals of full blown sleep apnoea are a dominant mechanism of at least the well recognised symptom of excessive daytime sleepiness, the high work of breathing (which is predominantly wasted work) may in its own right be a cause of many more subtle symptoms.

Similarly, it is not known which, or which combination, of the many physiological, hormonal and neurochemical changes induced in the snoring and sleep apnoea cycle lead to the various pathological outcomes. Is it the hypoxia, the oscillations in arterial carbon dioxide, the arousals and the accompanying surges of autonomic activity, the pressure changes within the thoracic cavity, the blood pressure variations or the many other changes that have been described? Which is the dominant trigger to sleepiness, to hypertension, to myocardial infarction and stroke? The simple answer is that we do not know and we largely assume the links exist. The advent of a non-invasive treatment device (nasal CPAP) has provided a method of measuring how many physiological variables change when the patient with sleep apnoea is permitted to sleep and breathe simultaneously.

Cardiovascular consequences of sleep apnoea and snoring

Many studies have now reported an association between systemic hypertension and heavy habitual snoring.^{8 9 14 17 18} When age and body mass index (BMI) are accounted for, however, results have varied as to whether snoring alone remains an independent risk factor for systemic hypertension. Thus, while Koskenvuo *et al*⁸ reported significantly greater odds ratios for hypertension in both male and female snorers than in non-snorers matched for age and BMI, others have failed to show significant differences when these confounders are allowed for.^{10 18}

Community based studies looking at sleep apnoea have pointed towards an association between this condition and systemic hypertension, independent of age, BMI, or other recognised confounders.^{5 19} The mechanism for this is not fully determined but there is evidence to indicate a role for the sympathetic nervous system in the pathophysiological process. Increased muscle sympathetic nerve activity has been recorded during sleep and wakefulness in subjects with obstructive sleep apnoea,^{20–22} with surges in sympathetic nerve activity being seen at the end of each apnoeic episode²³ accompanied by large rises in systemic arterial blood pressure. Furthermore, the increased levels of muscle sympathetic nerve activity diminish with nasal CPAP therapy.^{24 25}

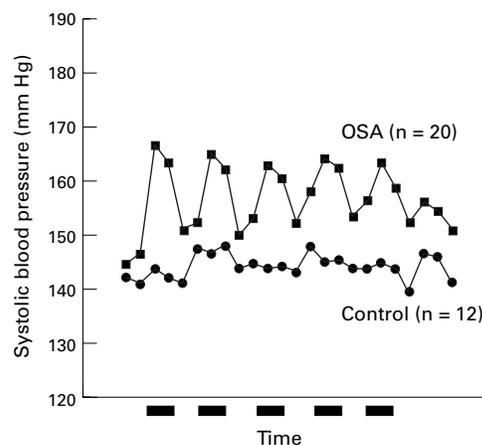


Figure 1 Mean systolic blood pressure (SBP) response to repetitive isocapnic hypoxia in 20 normotensive men with severe OSA (mean respiratory disturbance index 70 events/min) and normal daytime arterial blood gases (squares) and 12 non-apnoeic normotensive male control subjects (circles). All measurements were made in the awake state. Solid bars on the x axis represent each two minute period of isocapnic hypoxia. Each point represents the mean value for systolic blood pressure during a one minute period. Note the marked pressor response in the group with OSA seen with each hypoxic stimulus, and the significant increase in SBP during normoxia at the completion of the five stimuli. In contrast, the non-apnoeic subjects showed no significant change in SBP during the test.

The explanation, however, of the links between hypertension and sleep apnoea is likely to be much more complex, and recent work has also shown abnormalities in endothelium-dependent vascular relaxation in hypertensive patients with sleep apnoea compared with non-hypertensive patients with equally severe disease.²⁶

There is evidence that, even in the absence of daytime systemic hypertension, individuals with significant obstructive sleep apnoea show an abnormal pressor response to isocapnic hypoxia.²⁷ We have recently measured the daytime awake blood pressure response to repetitive short episodes (two minutes each) of isocapnic hypoxia (arterial oxygen saturation 80%) in 20 normotensive men with severe obstructive sleep apnoea. All showed a significant pressor response to each of the hypoxic stimuli that was not seen in a control group of non-apnoeic men (fig 1). Thus, the pattern of hypoxic stimulus is capable of producing large swings in blood pressure, even independently of the hypercapnia and arousal accompanying each episode, which suggests that it plays a part in the acute and possibly long term cardiovascular changes seen in this condition.

Once again, while the pathophysiological basis of the link is unknown, an association between obstructive sleep apnoea and acute myocardial infarction may also be found in the literature.²⁸ Whether the mechanism relates to increases in sympathetic nervous system activity, surges of arterial blood pressure related to obstructive episodes with resulting atheromatous plaque rupture, or to the abnormalities in fibrinolytic activity recently reported in some patients with sleep apnoea²⁹ is still under investigation. Although it is not the focus of this symposium, the literature also points to a higher incidence of stroke in patients with

snoring³⁰⁻³² and obstructive sleep apnoea,³³⁻³⁵ possibly through similar mechanisms.

In the setting of these facts and controversies this symposium aims to consider in more detail the evidence for a potential link between sleep apnoea, sleep disordered breathing, and cardiovascular disease, and to look at the pathophysiological mechanisms believed to be involved in bringing about an increased cardiovascular morbidity and mortality within this group of patients.

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