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Review

Sleep apnoea and systemic hypertension

Gross obstructive sleep apnoea has two clear consequences, recurrent sleep disruption (with daytime sleepiness) and repeated noctural hypoxaemia. The importance of the hypoxaemia is debated but when it is severe, or perhaps in the presence of ischaemic heart disease, it may trigger off serious arrhythmias.[1] When associated with even quite mild lower airways obstruction, obstructive sleep apnoea may lead to diurnal hypoxaemia and hypercapnia[2,3] with all the well known sequelae of fluid retention, pulmonary hypertension, and right ventricular hypertrophy (cor pulmonale).[4] Why profound intermittent hypoxaemia may apparently be harmless is not clear, but the key may be in its short duration and the recovery of arterial oxygen tension (Pa_{O_2}) between episodes of apnoea. For example, this pulsatile hypoxaemia does not lead to raised erythropoietin concentrations,[5] which explains the rarity of polycythaemia in obstructive sleep apnoea until daytime Pa_{O_2} is also low.

What this recurrent asphyxia of obstructive sleep apnoea does do, however, is to cause profound recurrent changes in haemodynamics. A rise in systolic blood pressure during the course of an episode of apnoea, with a further increase on arousal and termination of the apnoea, was documented early in the history of obstructive sleep apnoea.[6] Thus, whereas normally sleep is associated with a low and relatively stable systolic blood pressure,[7] in obstructive sleep apnoea arterial pressure is higher on average and oscillates considerably.[8] The early finding that many patients with obstructive sleep apnoea had diurnal systemic hypertension[9] led most workers to assume that this was a consequence of recurrent cardiovascular instability during sleep. This premise led some authors to search for hidden sleep apnoea among patients with essential hypertension, and to look for epidemiological evidence that people with a history of snoring (a marker of possible obstructive sleep apnoea) might be at greater risk of cardiovascular events such as stroke, angina, and myocardial infarction. Indeed, the suggestion has even been made that snoring alone, through bigger swings in pleural pressure and cardiac loading, might increase the risk of cardiovascular events in the absence of frank obstructive sleep apnoea. There are, however, many pitfalls and problems with these experimental and epidemiological data, which call for careful scrutiny before health screening programmes start to label snoring as more than an auditory nuisance.

This review divides the lines of argument and evidence into five parts: (1) How does obstructive sleep apnoea raise systemic blood pressure acutely? (2) Does obstructive sleep apnoea really raise diurnal systemic blood pressure in the long term and increase cardiovascular complications? (3) What is the evidence that an important proportion of patients with essential hypertension have appreciable sleep apnoea? (4) What is the epidemiological evidence that snoring is an independent risk factor for systemic hypertension and cardiovascular events? (5) What evidence do we need to establish whether snoring and sleep apnoea are important and underdiagnosed causes of essential hypertension or cardiovascular events?

How does obstructive sleep apnoea raise systemic blood pressure acutely?

During normal non-REM sleep systolic blood pressure is about 5–14% lower than during relaxed wakefulness.[7] The pressures are not constant but show smooth oscillations with 20–30 second cycles.[10] Blood pressure is higher during REM than non-REM sleep but does not reach the awake levels.[7,11].

With the onset of obstructed inspiratory efforts the recurrent falls in pleural pressure (sometimes as low as -80 cm H_2O) are reflected to a varying extent as recurrent dips in the systolic blood pressure.[8] Because the heart is in the chest, pleural pressures are added to and subtracted from the systolic blood pressure (pulsus paradoxus). They are not, however, fully reflected in systolic blood pressure swings owing to a complicated net effect of other factors and compensatory measures.[12] As the apnoea progresses systolic blood pressure rises and this is thought to be due to the concomitant fall in arterial oxygen saturation (Sa_{O_2}). The systolic blood pressure rise mirrors the fall in Sa_{O_2}, as does the accompanying bradycardia. Whether the rise in blood pressure is a direct consequence of the hypoxaemia, or the hypercapnic acidosis, or is due to the increased (albeit frustrated) respiratory effort that these provoke is not clear. So called "irradiation" of the cardiovascular centre from the respiratory centre may be responsible. The accompanying bradycardia is only partially accounted for by the hypoxaemia, as it

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requires apnoea (no lung expansion) and may be part of the diving reflex.[11 13] Stimulation of the carotid body, in the absence of stretch receptor activity, produces bradycardia.[14] During awake held inspiratory manoeuvres (Mueller) patients with obstructive sleep apnoea develop bradycardia apparently irrespective of any accompanying hypoxaemia.[15] In this study, however, the degree of hypoxaemia was much less (4% fall in Sao_2) than that experienced by the patients during their episodes of sleep apnoea of similar length (9% fall in Sao_2), and a maintained Mueller manoeuvre is not at all like obstructive sleep apnoea, where the inspiratory efforts are phasic until the apnoea breaks.

At the moment of arousal and termination of an episode of apnoea there is a further rise in systolic blood pressure, probably as a result of the release of the bradycardia (by stretch receptor activity), the rise in sympathetic output occurring with arousal, and the continuing fall in arterial oxygenation—which, of course, takes a further 10–12 seconds to reverse at the carotid body (and brain) owing to the circulation time.

On average systolic blood pressure usually rises about 1 mm Hg for every 1% fall in Sao_2 and the diastolic pressure rises about 0·5 mm Hg.[8] This is not always the case and falls in systolic blood pressure have been observed in association with apnoea in older patients.[16]

The fall in Sao_2 and rise in systolic blood pressure are associated with a rise in sympathetic nervous output[17] and catecholamine production.[18 19] Thus much of the rise in systolic blood pressure is likely to be due to peripheral vasoconstriction, as cardiac output has been shown to fall during the episodes of apnoea, a result mainly of the bradycardia, though stroke volume may also fall.[20]

The recurrent subatmospheric pleural pressures during each episode of obstructive apnoea, down to a certain pressure at least,[21] will aspirate venous blood into the right heart, and this may cause deviation of the interventricular septum and embarrassment of left ventricular filling by reducing its compliance.[22 23] On the other hand, the left ventricle will also be subjected to a similar dilating force and thus a higher preload. There is fluoroscopic evidence that both the left and the right heart enlarge during obstructive apnoea.[24] If left ventricular transmural pressure stayed constant, the fall in systolic blood pressure would equal the fall in pleural pressure. Starling's law of the heart, however, will offset this to some extent if the left ventricle can dilate. The rising peripheral resistance will present a raised afterload insofar as systolic pressure is maintained. Whether these recurrent falls in intrathoracic pressure have any permanent effect on cardiovascular function is not clear. The changes in blood pressure are all in the range that might be expected during exercise, but clearly for those pressures to be maintained throughout the night is extremely abnormal.

Recent evidence suggests that patients with obstructive sleep apnoea do have left ventricular hypertrophy,[25] but it is difficult to separate the relative contributions of nocturnal hypertension, diurnal hypertension, and obesity.

Does obstructive sleep apnoea really raise diurnal systemic blood pressure in the long term and increase cardiovascular events?

Whether the systemic hypertension that occurs during recurrent apnoea is carried over to the waking hours is by no means clear. Periods of stress from other causes that release catecholamines are thought to cause sustained hypertension,[26] and increased sympathetic activity is thought to underlie much essential hypertension.[27] Excess sympathetic activity may also raise blood lipid concentrations.[28]

The prevalence of systemic hypertension in patients with obstructive sleep apnoea in most series exceeds 40%.[9] Even in severe obstructive sleep apnoea the hypertension is often only moderate, however. Until recently the obstructive sleep apnoea was assumed to be the main cause but the confounding variable of obesity (or, more particularly, upper body obesity) was rarely considered. As most patients with obstructive sleep apnoea are obese it is difficult to be sure which factor is causing the hypertension. In a recent report Hoffstein *et al*[29] used multiple linear regression to dissect out the contributory causes of hypertension; obesity proved to be the dominant factor, apnoea severity being very much of secondary importance. Of 372 patients who snored, 194 had sleep apnoea (> 10 events/hour of sleep). Eight per cent of the variance in diastolic blood pressure in the group was accounted for by body mass index (weight/height^2, W/H^2), 4% by age, and only 1·7% by number of apnoeic episodes/hour of sleep. In an epidemiological survey that identified 15 individuals with obstructive sleep apnoea, the prevalence of hypertension was no higher in the 15 subjects with sleep apnoea than in 46 without.[30]

After effective treatment for obstructive sleep apnoea (mainly in obese patients) the blood pressure falls to some extent, but not to normal.[31] There are no good data to show a significant fall in diurnal systemic blood pressure after the institution of nasal continuous positive airway pressure (CPAP). The ability to apply or remove nasal CPAP offers an excellent opportunity to study the blood pressure changes, both short and long term, in patients with obstructive sleep apnoea.

Evidence has been presented recently that cardiovascular death rates are higher in untreated patients with obstructive sleep apnoea than in those treated by tracheostomy[32] or nasal CPAP.[33] It is, however, difficult to get a properly matched control group for this kind of study, and of course the cardiovascular deaths were not necessarily due to diurnal hypertension.

Pickering has recently reviewed the evidence that the risk from hypertension increases progressively as blood pressure increases, and concludes that the whole 24 hour blood pressure profile should be regarded as the risk factor and not a single measurement.[34] Whether obstructive sleep apnoea produces a small rise in diurnal blood pressure for 16 hours may therefore be less important than the much bigger rises that occur during the eight hours of sleep, the time when there is normally a fall in blood pressure.[7]

What is the evidence that an important proportion of patients with essential hypertension have appreciable sleep apnoea?

Essentially six studies have investigated whether there are occult cases of sleep apnoea among patients initially diagnosed as having essential hypertension. The first four found that 30–40% of such patients may have unexpected sleep apnoea and this was advanced as a possible explanation for their hypertension. Lavie *et al*[35] studied 16 hypertensive patients with a history suggesting sleep apnoea (out of a total of 50) and found that 11 (eight with predominantly obstructive apnoea) had more than 10 apnoeic episodes an hour. Five were more than 20% overweight and there was no control group of equal age and obesity. In addition, all the subjects were receiving drugs for their hypertension and these may provoke sleep apnoea, both central and obstructive.[36] Finally, there was no report of hypoxaemia or arousals accompanying the apnoea. Kales *et al*[37] compared 50 hypertensive patients and 50 control subjects matched for age and sex but not obesity. Most of the patients had refractory hypertension and were having several drugs, and 12 had left ventricular hypertrophy. Thirty per cent of the hypertensive patients had sleep apnoea (more than 30 episodes per night) but on average it was not severe (mean 22·4 episodes/hour in those with sleep apnoea, range 5–66). The amount of sleep apnoea was related to obesity and 40% of the patients were more than 20% overweight. No data on the controls' weights are given. Finally, the level of blood presure in the patients was not correlated with the severity of sleep apnoea at the time of the study. Fletcher *et al*[38] compared 46 men with essential hypertension (most having treatment) with 34 age matched and nearly weight matched control subjects (117% versus 112% overweight). Fourteen hypertensive men (30%) and three control subjects (9%) had more than 10 episodes of apnoea an hour, but were symptom free. The subjects with apnoea were heavier than the rest. Treatment for sleep apnoea lowered diastolic pressure by 5 mm Hg but there was no untreated control group. Williams *et al*[39] studied 23 hypertensive subjects (all having treatment) and eight age and weight matched control subjects. Three hour morning nap studies in hospital were used to examine respiratory movements and arterial oxygen saturation alone, after as much sleep deprivation as possible the night before. Thirty five per cent of the hypertensive subjects were classed as having sleep apnoea and they were much more obese than the non-apnoeic patients. Sleep deprivation, light sleep (probably a feature mainly of this short morning study in unfamiliar surroundings), and hypertensive medication may have artificially increased the prevalence of sleep apnoea—which in addition was not classified into obstructive and central.

Warley *et al*[36] studied 30 untreated hypertensive men with 30 control subjects matched for age, weight, height, smoking habit, and alcohol consumption, using pulse oximetry in their own homes. Despite a clear difference in blood pressure there was no difference in the amount of nocturnal hypoxaemia, suggesting no difference in the amount of significant sleep apnoea. A larger and more recent study reported the results of full sleep studies on 175 hypertensive patients (75 untreated) and 110 normotensive men.[40] There was no relation between blood pressure and the severity of sleep apnoea in the untreated hypertensive and control subjects. Interestingly, the subjects with treated hypertension had higher levels of sleep apnoea. Overall, the sleep apnoea levels were surprisingly high but the average body mass index of the untreated hypertensive group was 28·5 (normal 20–26) and the average age was 50.

This last study is the largest study of untreated hypertensive subjects. The higher apnoea rates found in the treated group suggests that concurrent treatment may have distorted the comparisons in some of the previous studies. Possible explanations for this include the induction of a metabolic alkalosis with diuretics[41] (particularly with inadequate potassium replacement), upper airway muscle suppression by α methyldopa[42] or beta adrenoceptor blocking drugs,[43] or even changes in the central control of respiration. Thus there is no incontrovertible evidence that sleep apnoea is significantly more common in hypertensive individuals once age and obesity are taken into account. The issue is further confused by a report at a recent conference[44] that treatment of hypertension with angiotensin converting enzyme inhibitors in a patient with sleep apnoea lessened apnoea severity. Whether this was due to an improvement in cardiac

output and removal of periodic breathing due to reduction of heart failure is not clear.[45]

What is the epidemiological evidence that snoring is an independent risk factor for systemic hypertension and cardiovascular events?

Most of the evidence that snoring is an independent risk factor for hypertension and other cardiovascular complications comes from large Finnish surveys and an earlier Italian survey. Lugaresi *et al*[46] collected health questionnaire data on 5713 men and women, who then had their blood pressures measured during a free health screen provided by the government. Systemic hypertension was correlated with older ages, obesity,[5] and snoring. Once account was taken of obesity, however, snoring had no independent effect on hypertension in the group more than 15% overweight, although in a thinner group blood pressures were higher in snorers. Whether the weight of the snorers was still on average higher than that of the non-snorers, however, is not clear. Snoring may be acting as a marker for obesity in these circumstances. Snoring has also been shown to be correlated with obesity, cigarette smoking, and the use of alcohol or hypnotics[47] and may therefore be a complex marker of aspects of "unhealthy" living. Whether exercise and fitness also affect snoring is not known. Koskenvuo *et al*[48] used a postal questionnaire (3847 men and 3664 women aged 40–69 years) to identify self reported snoring and self reported hypertension. They found a risk ratio (snorers versus non-snorers) of 2·68 for hypertension, which fell to 1·94 after allowance had been made for age and body mass index. A similar fall in risk ratio for angina, myocardial infarction, and admissions for ischaemic heart disease occurred when age and body mass index were taken into account. The 95% confidence intervals were not given but were above 1. Cigarette smoking was not taken into account, though this is a risk factor for most of the end points chosen. Norton and Dunn[49] surveyed 2001 patients in general practice, assessing the prevalence of snoring and any association with 13 common medical conditions. For 11 of these conditions a significant association with snoring was noted. The risk ratio for snorers for hypertension was about 2 after correction for age but not obesity. Interestingly, a history of snoring was found to be correlated with obesity, smoking, chest disease other than asthma, depression, alcoholism, rheumatism, and allergies. This suggests that snoring is a fairly non-specific marker of various diseases. In a further random sample (4064 men aged 30–69 studied by questionnaire by Gislason *et al*[30]) snoring was related to age and obesity. The prevalence of snoring was higher in the 9·3% of subjects who reported a history of hypertension. In the group as a whole snoring was not a risk factor for hypertension independently of obesity, but in the 40–49 year old group it was a significant though small extra predictive factor. In a case-control study Partinen and Palomaki looked at the snoring history of 50 men with cerebral infarction and 100 men with other disorders.[50] The groups were fairly well matched for weight but no allowance was made for alcohol consumption or cigarette smoking. The risk ratio (habitual snorers versus non-snorers) was up to 10 for cerebral infarction. There were, however, no differences in the prevalence of hypertension, coronary heart disease, or myocardial infarction between the two groups. The same group[51] also looked at the prevalence of self reported hypertension and snoring in a questionnaire survey of 4388 men aged 40–69. Hospital records and death certificates were subsequently checked over the following three years for admissions or deaths due to ischaemic heart disease or stroke. After adjustment for age, body mass index, history of hypertension, smoking, and alcohol consumption there was a relative risk of about 2 for ischaemic heart disease, and the risk for ischaemic heart disease and stroke combined was 2·08 ($p < 0·01$). This study provides the most convincing evidence of a relation between snoring and cardiovascular events, though if snoring is a marker for an unidentified risk factor there is still a problem.

Over the past few years it has been recognised that W/H^2 is not the measure of obesity that correlates best with cardiovascular events. Blair *et al*[52] and others[53 54] have shown that upper body obesity is a better predictor of hypertension than overall obesity. Stroke also correlates better with waist to hip ratio than W/H^2.[55] Thus the use of W/H^2 is unlikely to correct fully for the contribution made by obesity to hypertension and some cardiovascular diseases or deaths. In an unfinished survey of 480 normal men we have shown[56] that snoring and overnight hypoxaemic dipping correlate better with neck circumference than W/H^2. We[57] and others[58] have also found that the degree of obstructive sleep apnoea in patients referred to a sleep clinic also depends more on neck circumference than W/H^2. Thus snoring may also to some extent be a better marker of the greater obesity risk—the upper body distribution of fat. This means that snoring is a very complex marker of several cardiovascular risk factors—obesity, upper body obesity, smoking, age, alcohol consumption, and perhaps other aspects of health as well. At present we have to agree with a recent review[59] that the case for snoring as an independent cause of vascular disease is far from proved. If it proves to be an independent risk factor, it is likely to operate through the changes in cardiovascular physiology that occur during sleep rather than through diurnal hypertension.

What evidence do we need to establish whether snoring and sleep apnoea are important and underdiagnosed causes of essential hypertension or cardiovascular events?

We must first find out what factors can provoke snoring that could in themselves affect cardiovascular disease. These must then be accounted for in epidemiological surveys before a claim that snoring is an independent risk factor can be substantiated. If snoring does prove to be an independent risk factor it will be important to establish whether snoring alone is important, or whether it acts as a marker for a smaller subset of subjects with obstructive sleep apnoea. This will be arduous but important if we are to suggest that snoring is in itself a health hazard worthy of attention. Should daytime hypertension prove to be a necessary intermediary between snoring (or obstructive sleep apnoea) and cardiovascular events, daytime blood pressure measurement would be an adequate screening tool; if not, then screening would be difficult since self reporting of snoring is not likely to be particularly reliable.

In conclusion, the case for an important causal link between sleep disordered breathing or snoring and hypertension or cardiovascular events is far from proved, though there are good theoretical reasons for suspecting that such a link might exist.

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