

SLEEP APNOEA AND HYPERTENSION: PROOF AT LAST?

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Introductory article

Prospective study of the association between sleep-disordered breathing and hypertension

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Background: Sleep-disordered breathing is prevalent in the general population and has been linked to chronically elevated blood pressure in cross-sectional epidemiologic studies. We performed a prospective, population-based study of the association between objectively measured sleep-disordered breathing and hypertension (defined as a laboratory-measured blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications). *Methods:* We analyzed data on sleep-disordered breathing, blood pressure, habitus, and health history at baseline and after four years of follow-up in 709 participants of the Wisconsin Sleep Cohort Study (and after eight years of follow-up in the case of 184 of these participants). Participants were assessed overnight by 18-channel polysomnography for sleep-disordered breathing, as defined by the apnea-hypopnea index (the number of episodes of apnea and hypopnea per hour of sleep). The odds ratios for the presence of hypertension at the four-year follow-up study according to the apnea-hypopnea index at baseline were estimated after adjustment for baseline hypertension status, body-mass index, neck and waist circumference, age, sex, and weekly use of alcohol and cigarettes. *Results:* Relative to the reference category of an apnea-hypopnea index of 0 events per hour at base line, the odds ratios for the presence of hypertension at follow-up were 1.42 (95% CI 1.13 to 1.78) with an apnea-hypopnea index of 0.1 to 4.9 events per hour at baseline as compared with none, 2.03 (95% CI 1.29 to 3.17) with an apnea-hypopnea index of 5.0 to 14.9 events per hour, and 2.89 (95% CI 1.46 to 5.64) with an apnea-hypopnea index of 15.0 or more events per hour. *Conclusions:* We found a dose-response association between sleep-disordered breathing at baseline and the presence of hypertension four years later that was independent of known confounding factors. The findings suggest that sleep-disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population. (*N Engl J Med* 2000;342:1378-84)

BACKGROUND

The issue of whether obstructive sleep apnoea (OSA) causes diurnal hypertension has been a source of debate for over 20 years, since early case series of patients with OSA found a high prevalence of clinical hypertension.^{1,2} However, OSA and hypertension share a remarkable number of risk factors. In particular, hypertension is known to be related to obesity (dominantly upper body obesity^{3,4}), age,⁵ alcohol consumption,⁶⁻⁸ smoking,⁹ exercise levels,¹⁰ and caffeine consumption.¹¹⁻¹³ OSA is also associated with upper body obesity,¹⁴ age,^{15,16} alcohol consumption,¹⁷ and smoking¹⁸; such patients are sleepy,¹⁹ likely to take less exercise, and drink about three times more caffeine.²⁰ Disentangling these known confounding variables is extremely difficult, and this difficulty has been the main source of uncertainty over data published in this area.²¹⁻²⁶ Even if the known confounders can be allowed for, there may be others that have not yet been discovered. Our concern for unknown confounders is not entirely theoretical since the issue of increased caffeine consumption confounding blood pressure relationships in patients with OSA (presumably to try and alleviate sleepiness) has only very recently been explored.²⁰ Caffeine has been shown to have significant effects on blood pressure acutely; in one study non-coffee drinkers received 250 mg caffeine and, on average, their systolic blood pressure rose 14 mm Hg and the diastolic pressure 10 mm Hg.¹¹ In a second study 19% of subjects with blood pressure initially at the higher end of the normal range crossed the hypertensive threshold following 3.3 mg/kg of caffeine.¹² The effects of chronic caffeine consumption are less clear¹³ and, to our knowledge, there are no data on the effects of acute

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withdrawal such as might occur when the sleepiness caused by OSA resolves with nasal continuous positive airway pressure (nCPAP) treatment.

OSA clearly causes night time rises in arterial blood pressure²⁷ and this is not in dispute. It is whether there is a carryover effect into the day, with all the known detrimental effects of systemic hypertension, that is in question.

In addition to the problem of confounding variables, there are other difficulties to be surmounted. Neither hypertension nor OSA are well measured, leading to underestimates of any correlation between them. The difficulties in measuring hypertension are whether one-off or 24 hour assessments are better predictors of morbidity, variability in the measurement with time, and an uncertainty as to the most damaging aspect of hypertension (mean levels, variability, absence of nocturnal dipping²⁸). The measurement difficulty for OSA occurs, not only because of considerable night to night variation,²⁹ but also because it is unclear what pathophysiological feature might be a hypertensive agent. For example, is it really the apnoeas, or might it be any associated nocturnal hypoxaemia (perhaps related to its episodic nature, the mean levels, or falling below critical thresholds), sleep fragmentation, increased pleural pressure swings, or maybe small rises in Paco_2 ? Thus, designing experiments or surveys to confidently establish causal links between OSA and hypertension, and then extrapolating to infer excess morbidity and mortality, is a task littered with pitfalls. For these reasons such studies require detailed scrutiny before they should be allowed to influence clinical practice. A review of the methodological problems of such studies has recently been published.³⁰

Over the last two years there have been several papers that have attempted to control for, and avoid, errors due to confounding variables and other problems. First have been simulations of OSA, or aspects of OSA, thus providing matched control data with which to compare any effects due to the OSA itself. Particularly elegant are the animal studies on dogs in Phillipson's laboratory in Toronto, showing that acute onset simulated OSA clearly raises daytime blood pressure over a few months by up to 15 mm Hg, which falls again when normal nocturnal breathing is allowed to return.³¹ Replicating just the sleep fragmentation, although similarly raising sleeping blood pressure, did not lead to a rise in awake blood pressure.³² This therefore suggested that the attendant hypoxaemia, hypercapnia, or increased pleural pressure swings—alone or in combination—were the likely pathophysiological mechanisms. More recently the same group have shown that similar periods of simulated OSA in dogs impair left ventricular systolic performance, measured during wakefulness by echocardiography.³³

Studies on rats have implied that episodic hypoxia can raise awake blood pressure,³⁴ although this effect is strain dependent, suggesting the potential for different physiological responses in different species. The rise in awake blood pressure is of the order of 12 mm Hg and is blocked by carotid body denervation, sympathetic nerve ablation, renal sympathectomy, adrenal medullectomy, and an ACE inhibitor.³⁵ Additional hypercapnia did not seem to increase the awake hypertensive effect of hypoxia. In humans a period of acute nocturnal hypoxia (using hypobaric chambers) leads to a rise in heart rate and blood pressure for about two hours after removal from the hypoxia, compared with controls, but only in some individuals.³⁶ This particular experiment did not fully control for the differences in the degree of sleep fragmentation, and hypocapnia (rather than hypercapnia) would have attended the hypoxia. The authors concluded that peripheral chemoreceptor stimulation was the likely explanation via increases in

sympathoadrenal activity (as evidenced by increased levels of overnight urinary adrenaline but not noradrenaline), a phenomenon already reported to occur at real altitude in less well controlled experiments.³⁷ The known interindividual variations in hypoxic chemosensitivity³⁸ might then possibly explain the interindividual variation in the hypertensive effect of hypoxia found in the hypobaric chamber study.

Many authors have used clinic based case series to try to prove an association between OSA and diurnal hypertension. These have always fallen prey to the criticism that there has been inadequate controlling for confounders. They have usually employed multiple regression modelling techniques to try to unravel independent associations. In general, the more the controlling, the less is the independent effect of OSA on blood pressure.³⁹ An unavoidable consequence of this approach is that true cause and effect within closely correlated variables such as obesity, blood pressure, and OSA are difficult to establish. For example, if much of the previously established association between blood pressure and obesity was in fact due to the presence of OSA as the true causal factor, then allowing for obesity first in multiple regression techniques will falsely lower the contribution of OSA to the variance in blood pressure. However, most well controlled series have suggested that OSA is more likely to be an independent risk factor for hypertension in younger patients.^{40–41} A more recent study by Lavie *et al* studied 2677 patients who had attended a specialist sleep clinic over a 10 year period.⁴² Confounders considered were smoking, alcohol use, age, and body habitus (including markers of upper body obesity), but exercise and caffeine consumption were not considered. Hypertension was defined as $>140/90$ or treatment with hypotensive medications, although a separate analysis was performed excluding subjects on such drugs. When corrected for age, sex and neck circumference (the most influential marker of obesity on blood pressure in this study), the apnoea-hypopnoea index (AHI) remained significantly related to both diastolic ($r^2 = 0.22$) and systolic ($r^2 = 0.20$) pressure. This model predicted that a subject with an AHI of 60 should have a systolic pressure 6 mm Hg higher and a diastolic pressure 5 mm Hg higher than a matched subject without OSA. The authors reported similar results when indices of nocturnal hypoxia were used.

Another approach to bypass the problems of confounding variables has been the use of case control studies. Davies *et al*⁴³ matched 45 patients with OSA to 45 control subjects without OSA from the community. They were matched for age, sex, obesity, alcohol consumption, cigarette usage, prevalence of diabetes, and a prior history of hypertension and ischaemic heart disease. The matching was difficult as, not surprisingly, many subjects matched to patients with OSA had degrees of OSA themselves and had to be discarded. The 24 hour blood pressure data showed that the patients with OSA were clearly more hypertensive than the control subjects (average daytime diastolic pressure 4.6 mm Hg higher), although this difference was less in the afternoon and greatest in the more immediate post-sleep period. This morning dominance of the OSA hypertensive effect had been noted previously.^{44–45} Unfortunately, this case control study was performed before the data on greater caffeine consumption in patients with OSA were available,²⁰ and levels of physical activity were not controlled for.

Yet another further approach to circumvent confounding variables has been to assess treatment effects following the provision of nCPAP. This approach uses the patient as his own control, but requires a valid placebo treated control group as well. In addition, the effects of OSA on blood pressure might not be reversible in the short term, if at all,

and a negative result might lead to incorrect assumptions as to the size of any OSA effect. Furthermore, such studies assume that any difference between treatment and control will be due directly to the treatment alone. However, following treatment of OSA, resolution of the sleepiness¹⁹ may have secondary effects on exercise levels and caffeine consumption for which it is difficult to control. However, three controlled studies of 24 hour blood pressure in patients suffering from OSA treated with either active nCPAP or a placebo have recently been carried out,^{46, 47} (Becker HF, Marburg, personal communication), all of which have shown significant falls in awake blood pressures (in the region of 5 mm Hg), again particularly in the morning, compared with control patients. Two of these studies found that the fall in blood pressure during nCPAP treatment is greater in patients in whom the original OSA is most severe, and one has suggested that those already on hypotensive agents have a larger fall in blood pressure (unpublished observations). These falls in blood pressure are of a similar magnitude to those seen in many trials of antihypertensive agents.⁴⁸

Introductory article

Finally, we come to community based epidemiological studies where every attempt has been made to control for all known confounding variables. The introductory article by Peppard *et al*⁴⁹ is one such piece of work. In 1989 Young and her associates in Wisconsin started looking at a community based population of adult men and women with overnight polysomnography. The population actually studied in this way was enriched for likely OSA according to the results of six pertinent questions from a four page questionnaire on sleep habits and health history.¹⁶ The work provided data on the prevalence of OSA and its association with a variety of potential causes and consequences such as body weight,⁵⁰ sleepiness,¹⁶ car accidents,⁵¹ and hypertension.⁵²⁻⁵⁴ A conventional measure, AHI, was used to define the presence of OSA, although an obstructive cause for any apnoeas and hypopnoeas was not confirmed but was assumed. Hence, Young and associates are careful to refer to sleep disordered breathing rather than OSA.

The study by Peppard *et al* is essentially a cross sectional study looking at casual blood pressure and relating these figures to sleep study data gathered four years previously. In fact, because second sleep studies were done after four years (n=709) with blood pressure data also recollected in a subgroup at eight years (n=219), there were more four year data points (n=893) than subjects (n=709) because 219 subjects had provided more than one set of data, having been studied over two sequential four year periods. This approach of using blood pressure measurements four years on from the sleep study was taken as it was assumed that blood pressure might take some time to rise in response to OSA, and thus a stronger relationship would be likely.

Hypertension was assumed if hypotensive drugs were being prescribed or if the casual blood pressure was above a certain threshold: >140/90 for the main analysis although data for >160/100 were also reported (approximately half of those defined as hypertensive were receiving hypotensive therapy). The subjects were put into four groups according to the AHI score at the beginning of the four year follow up period: AHI 0/h (n=187), AHI 0.1-4.9/h (n=507), AHI 5.0-14.9/h (n=132), and AHI $\geq 15/h$ (n=67). The mean blood pressures at the four year follow up (and the baseline values) in these four progressively more apnoeic groups were: 118/75 (120/79); 123/79 (124/82); 131/82 (130/84); and 129/81 (135/88). Note that in the group with the most severe apnoea (AHI $\geq 15/h$)

the mean blood pressures four years later were no higher than baseline values, which suggests that an AHI of $\geq 15/h$ for four years may not further raise blood pressure significantly. However, an explanation for this may be that a higher proportion of this group had started hypotensive drugs during the previous four years (9/67 (13.4%) compared with 47/826 (5.7%) in the other groups, p=0.05), although it is not clear from the paper whether knowledge of the initial blood pressure or AHI influenced subsequent physician management and thus the likelihood of being prescribed hypotensive drugs.

The main purpose of the study was to see if AHI was an independent predictor of the prevalence of hypertension. Using a blood pressure of $\geq 140/90$ mm Hg (or on hypotensive drugs), the prevalence of hypertension in the four OSA severity groups was 17%, 28%, 48%, and 60%; and using a blood pressure of $\geq 160/100$ (or on hypotensive drugs), the prevalence estimates were 10%, 17%, 28%, and 49%. Thus, hypertension was in the region of four times more common in the group with the highest AHI than in those with the lowest AHI (it is worth noting that most cases of hypertension in the former group were defined by hypotensive drug usage and, indeed, the *actual* blood pressure levels were slightly lower in the group with the highest AHI than in those with the second highest AHI, see previous paragraph). Needless to say, the group with the highest AHI was also more obese than the group with the lowest AHI (body mass index (BMI) 36 kg/m² v 29 kg/m²). The authors present odds ratio data for the presence of hypertension for the three groups of increasing levels of AHI activity compared with the lowest AHI group, progressively controlling for more and more potentially confounding variables. Figure 1 shows these progressively more corrected data for only the highest AHI group (AHI $\geq 15/h$) compared with the lowest (AHI 0/h). Although estimates of weekly exercise are referred to in the text, it is not specifically stated whether the reported odds ratios include controlling for this potential confounding variable. Furthermore, when this study was carried out, the effects of increased caffeine consumption in subjects with OSA were not known.²⁰ However, it is clear from this study that the presence of OSA remains a significant independent risk factor for daytime hypertension, even when most known confounding variables have been allowed for. It seems unlikely, although in theory possible, that other as yet unknown potential confounders would reduce the odds ratio to a point of statistical insignificance.

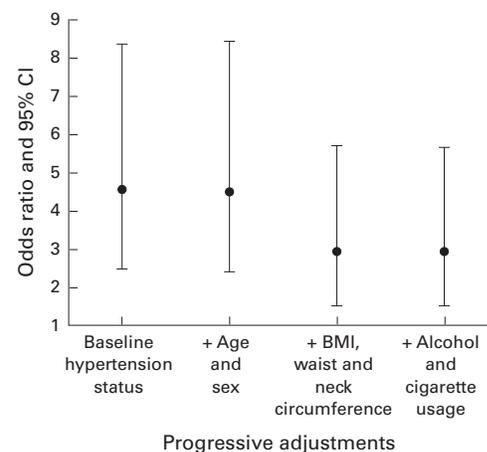


Figure 1 Odds ratios for the presence of hypertension according to OSA status (AHI $\geq 15/h$ versus AHI 0/h) with progressive adjustments for confounding variables. The final column allows for all the variables listed. From Peppard *et al*.⁴⁹

Learning points

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- ▶ Large arousal related transient rises in blood pressure occur at the end of each obstructive apnoea.
- ▶ Daytime hypertension is common in OSA but these conditions share many common risk factors and disentangling true cause and effect has been very difficult.
- ▶ Poor quantification of both hypertension and OSA will have reduced estimates of any potential correlation.
- ▶ Case control and treatment studies in OSA strongly suggest a significant carryover of hypertension into the day, mainly the morning.
- ▶ Epidemiological studies controlling for as many confounders as possible also strongly suggest that even small amounts of OSA are an independent risk factor for daytime hypertension.
- ▶ Potential candidates for provoking daytime hypertension in OSA are nocturnal hypoxia or hypercapnia, increased ventilatory effort, and sleep fragmentation; the latter seems the least likely explanation.

Lower odds ratios for the effect of AHI on hypertension than those found in the study by Peppard *et al* have been found in another large community based study published in 2000.⁵⁵ The Sleep Heart Health Study measured AHI in 6132 subjects and found that those with AHI values of ≥ 30 /h were 1.37 (95% CI 1.03 to 1.83) times more likely to have hypertension (blood pressures $\geq 140/90$ mm Hg or on hypotensives) than those with an AHI of <1.5 /h, after allowing for most potentially confounding variables. Measurements of hypoxia seemed slightly more predictive (odds ratio 1.46) but are likely to have been more robust than measurements of AHI.

Although the odds ratio of 2.89 found in the study by Peppard *et al* is not enormous, in terms of actual cases of hypertension it will have a profound effect given the overall high prevalence of hypertension and, to a lesser extent, OSA itself. For example, in the study population (not typical of the general population due to enrichment for sleep apnoea by prior questionnaire), the prevalence of hypertension (blood pressures of $\geq 140/90$ or on hypotensive drugs) in the group with the lowest AHI was 32/187 (17%) compared with 278/893 (31%) in the whole group. If we use the adjusted odds ratio, we can work out approximately how many extra cases of hypertension in the three higher AHI groups there might be as a result of this higher AHI activity. The calculation gives 120 cases of hypertension of 706 (17%) resulting from the “baseline” prevalence, about 80 from the confounding variables such as obesity, and an extra 78 from increased AHI. This is a truly staggering figure, implying, as it does, that perhaps almost one third of the cases of hypertension in this particular study population were possibly related to higher AHI values.

Elucidating the mechanism of this effect was not part of this study. However, the significant odds ratio in the low AHI group (0.1–4.9/h) is still significant (1.42) and difficult to understand. A few apnoeas per hour would seem unlikely to increase greatly the number of overall arousals per hour, which are already over 20 in most normal individuals during polysomnography,⁵⁶ and the hypoxic challenge is similarly likely to be trivial. It may be that the AHI is simply a marker of increases in upper airway resistance during sleep, representing as it does only the more severe end of the spectrum of pharyngeal narrowing during sleep. It may be that narrowing of the pharynx, with increased inspiratory effort (with or

without snoring), could act as a hypertensive agent, perhaps through increased pleural pressure swings (or hypercapnia) across much more of the night than the brief periods of actual apnoea or hypopnoea. There is some indirect evidence from three community population based studies that this could be the case.^{57–59} The increased inspiratory effort and subatmospheric pleural pressure will, on average, lower arterial blood pressure (pulsus paradoxus) through the night, and perhaps lead to compensation mechanisms to raise blood pressure that carry over into the day.

Conclusions

What then can we conclude, other than that 2000 was a bumper year for high quality studies on sleep apnoea and hypertension? It now seems almost beyond all reasonable doubt that OSA is an independent risk factor for diurnal hypertension, and that this has more than trivial consequences at a public health level. It is yet to be proven that hypertension due to OSA has the same adverse cardiovascular effects as hypertension from other causes.⁶⁰ This seems likely, but there is some preliminary evidence in this area to suggest it may not.⁶¹ Furthermore, until a better treatment for OSA is available, it seems unlikely that large numbers of asymptomatic individuals will use nCPAP to lower their blood pressure by about 5 mm Hg if there are no daytime symptoms to be improved as well. A hypotensive drug is likely to be the preferable alternative, and innumerable studies have shown the benefit from this approach.⁴⁸ Obesity is at the root of much of the cardiovascular pathology discussed here—either directly or via OSA—and should be the primary target for intervention. We urgently need effective strategies to prevent and reverse the serious problem of rising obesity. No one could argue that the mean (SD) BMI of 30 (7) kg/m² seen in the Wisconsin study is not a major health hazard of our time.

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