REVIEW SERIES

Sleep · 6: Obstructive sleep apnoea/hypopnoea syndrome and hypertension

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The use of CPAP to control excessive daytime sleepiness in OSAHS probably also produces a substantial reduction in vascular risk. This is reviewed with particular reference to hypertension.

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is primarily treated to improve quality of life by controlling excessive daytime sleepiness. However, treatment of this disorder probably also produces a substantial reduction in vascular risk—which would result in OSAHS treatment improving both patient survival and quality of life. This has been an area of intense interest for over 20 years, since it has proved challenging from the methodological viewpoint and because it hints at fascinating, possibly novel, physiological mechanisms. This review discusses this area with particular reference to hypertension and hypertensive vascular risk. Heart failure and Cheyne-Stokes breathing are not discussed as they are covered in other articles in this series.

SYSTEMIC HYPERTENSION

It is clear that patients with OSAHS have, on average, higher blood pressures than age and sex matched controls, and the strength of this relationship is striking. About 40% of patients with OSAHS are hypertensive while awake according to standard criteria,[1] and about 40% of patients with resistant hypertension have detectable OSAHS.[2]

Until recently there has been doubt as to whether this relationship is aetiological or due to a confounding association, particularly with obesity and body fat distribution. It has also been debated whether therapeutic interventions to treat OSAHS reduce blood pressure. The details of this debate are quite complex and are worth exploration since they are central to understanding the clinical dilemmas in this area, including patient treatment decisions.

OBESITY, FAT DISTRIBUTION AND OSAHS

The most difficult conundrum in understanding the link between OSAHS and blood pressure is the presence of significant obesity in most adult patients with OSAHS, and the tendency for this to be differentially distributed in the abdomen and upper body—probably producing much of its effect on sleep apnoea through the deposition of fat in the neck, narrowing the pharyngeal airway.[3] This pattern of ''upper body obesity'' typifies male fat deposition (and is probably why OSAHS is predominantly a male disease) and is known to be a major risk factor for hypertension, insulin resistance, and hyperglycaemia—the so-called syndrome X.[4 5]

Most, perhaps all, of the vascular risk attributed to obesity is actually attributed to upper body fat deposition rather than overall obesity.[6–8] The question is therefore whether this fat distribution pattern is actually the explanation for the raised blood pressure in patients with OSAHS rather than the OSAHS itself, or whether the OSAHS is directly the cause of the raised blood pressure (or possibly both). The usual research mechanisms for resolving such questions are the comparison of affected patients with phenotypically similar subjects without the disease but otherwise similar in their expression of confounding factors (case-control studies), or the statistical correction for the known confounders in large unselected samples (observational population sample/cohort studies). Both approaches have been applied to OSAHS and the major studies addressing these questions are summarised in table 1.

INTERPRETATION OF NON-INTERVENTIONAL BLOOD PRESSURE DATA

There are substantial and potentially insurmountable problems for case-control and statistically corrected studies in this area. These problems relate to the ways in which OSAHS severity and body fat quantity and distribution are quantified. Whether the study design requires the selection of well matched controls or depends on the use of statistical correction for confounding, the confidence in its conclusions will depend on the accuracy with which these factors are measured (in order to select well matched controls for a case-control study), or for entry into statistical analyses in population studies. Upper body obesity is typically quantified from crude indices such as the waist to hip circumference ratio or the ratio of the waist circumference to the subject's height.[4 5 9] In both cases a rising ratio indicates an increasing upper body fat pattern. Such indices are often used in statistical analyses to determine whether there is evidence of an independent association between blood pressure and OSAHS severity after considering the effect of fat distribution (quantified as one or both of these ratios).[10] A

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Abbreviations: AHI, apnoea/hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; OSAHS, obstructive sleep apnoea/hypopnoea syndrome

Table 1 Non-randomised studies of blood pressure and OSAHS

Study	Population	No of subjects	Sex (M/F)	Confounding variables considered	Comments
Kales[23]	Hypertensives and normal controls	50/50	37/13?	Age, sex	HT correlates with OSAHS severity
Fletcher[24]	Hypertensives and normotensive controls	80	80/0	Age, weight	AHI correlates with HT
Hoffstein[25]	Sleep clinic patients	372	310/62	Age, BMI, AHI	AHI is an independent predictor of BP
Warley[73]	Hypertensive patients	30	30/0	Age, BMI	No excess respiratory disturbance in HT
Jennum[26]	Severe OSAHS	14	13/1	None	BP falls with CPAP treatment
Stradling[27]	Community population	752	224/224	Age, BMI, smoking, alcohol	No independent predictors of BP identified
Millman[28]	OSAHS and population controls	1056/0	152/0 904/0	Age, BMI	High prevalence of HT in OSAHS related to age and obesity
Mayer[29]	Hypertensive OSAHS patients	12	12/0	None	BP falls with CPAP treatment
Rajala[30]	Obese patients	27	13/14	BMI, smoking	Fall in BP in hypertensives only
Naughton[31]	Sleep clinic patients	18	18/0	None	Nocturnal hypoxaemia predicts daytime BP
Mendelson[32]	Sleep clinic patients	619	619/0	Weight, age	More hypoxaemia (probably OSAHS related) in hypertensives
Gleadhill[33]	GP and hypertension clinic	34	34/0	Age, sex, BMI	Fall in BP with CPAP, greater effect in non obese
Rauscher[2]	Snorers	191	191/0	None	HT unrelated to sleep apnoea severity
Guilleminault[34]	Sleep clinic patients	10	10/0	None	AHI higher in hypertensives
Akashiba[35]	OSAHS patients	5	5/0	None	BP falls with CPAP treatment
Kiselak[36]	Hospital weight loss programme	19	9/10	None	Respiratory disturbance strongest predictor of BP
Lavie[37]	OSAHS patients	38	38/0	Age, BMI, wakefulness	Systolic BP higher in females with OSAHS
Bearpark[38]	Population sample	400	294/106	BMI, smoking, alcohol, sex	BP predicted by OSAHS severity
Grunstein[39]	Sleep clinic patients	1464	1464/0	Age, obesity	Fall in BP with effective CPAP treatment
Wilcox[40]	Sleep clinic patients	19	19/0	None	OSAHS is an independent predictor of BP
Carlson[41]	Sleep clinic OSAHS and non-OSAHS patients	664	294/370	Age, BMI	BP fall with CPAP in hypertensives only
Suzuki[42]	Sleep clinic patients	9	8/1	None	Greater fall in hypertensives with weight loss than CPAP
Rauscher[43]	OSAHS with HT	60	48/12	None	Nocturnal BP fall with CPAP
Marrone[44]	OSAHS patients	10	9/1	Unmatched controls	AHI is an independent predictor of BP
Hla[45]	OSAHS, snorers and non-snorers	147	75/72	Age, sex, BMI	AHI is an independent determinant of BP
Hoffstein[46]	Sleep clinic patients	1415	1026/389	Age, sex, BMI, snoring intensity	AHI is an independent determinant of BP
Strohl[47]	Sleep clinic patients	261	261/0	BMI	Nocturnal BP fall with CPAP treatment
Prybylowski[48]	OSAHS patients	22	21/1	None	AHI associated with hypertension
Davies[49]	Sleep clinic patients	19	19/0	Age, BMI, smoking, alcohol	Fall in nocturnal systolic BP with CPAP
Fernandez-Pinilla[50]	Sleep clinic patients	17	13/4	None	OSAHS is an independent predictor of BP
Schwartz[51]	Hypertensive OSAHS patients	7	7/0	None	Day and night BP higher in OSAHS than non-apnoeic snorers
Bartel[52]	Hypertensive and matched normotensive controls	20	4/16	Age, sex, BMI, neck size, sleepiness	Hypoxaemia in non-REM is the most potent predictor of diastolic BP
Mendelson[53]	OSAHS patients	518	430/88	Weight, age, sex	Higher BP in OSAHS than other sleep disturbances
Guilleminault[54]	Sleep clinic patients	334	334/0	Age, sex, BMI neck size	Fall in BP with CPAP treatment
Grunstein[55]	Obese patients	3035	1324/1711	Age, obesity, alcohol, smoking	BP associated with greater obesity in OSAHS patients
Pankow[56]	OSAHS and snorers	25	24/1	Age, sex, BMI	AHI is an independent predictor of BP
Olson[57]	Community population	441	?	None	Increasing HT with increasing respiratory disturbance
Nabe[58]	OSAHS patients	73	68/5	Age, BMI	OSAHS severity is a predictor of BP
Sforza[59]	Sleep clinic patients	253	221/32	Age, sex, BMI	No effect of CPAP on BP in hypertensives
Akashiba[60]	Sleep clinic patients	31	31/0	Age, sex, obesity	No change in BP with CPAP
Hedner[61]	Sleep clinic patients	12	10/2	None	Increasing systolic BP with OSAHS severity
Engelman[62]	Sleep clinic patients	13	11/2	None	CPAP has no effect on BP in heterogeneous patient group
Suzuki[63]	OSAHS patients and controls	6	5/1	Age, BMI, years of snoring	Initial BP fall with CPAP, not persisting after 3 weeks
Coy[64]	Volunteers, many with sleep problems	67	56/11	Age, BMI	OSAHS severity is the only predictor of diastolic BP
Saarelainen[65]	OSAHS patients	11	11/0	None	Fall in nocturnal BP with CPAP
Worsop[66]	Hypertensive and normotensive patients	93	81/12	BMI, age, sex, alcohol	Higher incidence of OSAHS in hypertensives
Grote[67]	Sleep clinic patients	1190	1087/103	Age, BMI,	Respiratory disturbance is an independent risk factor for HT
Lavie[68]	Sleep clinic patients	2677	1949/728	Age, BMI, sex	Severity of OSAHS predicts BP
Peppard[69]	Community population	893	504/389	HT, BMI, age, sex, alcohol, smoking	Increasing incidence of HT with increasing AHI
Davies[70]	OSAHS with matched controls	45	45/0	Age, BMI, HT, alcohol, smoking	Higher BP in OSAHS
Stradling[74]	Community population	448		None	Nocturnal respiratory effort independently predicts lack of nocturnal BP fall
Grote[71]	Hypertensive sleep clinic patients	591		Age	Increasing severity of HT with increasing respiratory disturbance
Logan[72]	OSAHS patients with refractory hypertension	11	10/1	None	Resolution of HT with CPAP treatment

AHI, apnoea/hypopnoea index; BMI, body mass index; BP, blood pressure; HT, hypertension; CPAP, continuous positive airway pressure; ?, not documented in publication.

persisting relationship is then taken as evidence of independent causality.

Unfortunately, OSAHS severity is influenced by characteristics in body fat distribution which are not captured by these simple ratios, and these distribution characteristics may be differentially associated with rises in blood pressure. Neck circumference is the strongest predictor of OSAHS severity of any of the simple body dimension indices so far studied,[3] and waist circumference (the main element in the crude ratio indices of upper body fat deposition) is not a robust predictor of neck size.[3] It is not known whether the subtleties of fat distribution that are important in inducing sleep apnoea are also preferentially important in producing syndrome X and so raised blood pressure. It is therefore impossible to know if correction for the simple indices of fat distribution is adequate to lead one to be confident that the apparently significant residual relationships between sleep apnoea severity and blood pressure (after correcting for obesity and body fat distribution) are sufficient to prove causality.

Equally important, though likely to result in an underestimate of the importance of OSAHS in causing raised blood pressure, are the measurement problems in the quantification of sleep apnoea itself. Traditionally the severity of OSAHS has been assessed by counting the number of episodes of respiratory disturbance per hour of sleep. Unfortunately, this is at best a semi-quantitative technique. The number of respiratory episodes per hour is heavily influenced by arbitrary thresholds in defining what is significant both in terms of the amount of physiological disturbance present (does transient partial pharyngeal collapse alone count, does it count if it is associated with arousal from sleep, is some fall in airflow through the upper airway needed and if so how much, and if complete airway obstruction is needed then for how long, etc) as well as the vagaries of measurement equipment and its interaction with the patient[11] and the variability in human scoring behaviour.[12 13] Finally, there is a substantial variation in the severity of sleep apnoea from night to night—particularly in the mid range of disease severity. All these factors mean that the relationship between the apparently ''simple'' index of respiratory disturbance and the symptomatic consequences of OSAHS are very loose.[14 15] This poor measurement precision, accuracy, and reproducibility will result in ''noise'' in the data gathered in the quantification of OSAHS which will greatly weaken its apparent correlation with other factors such as blood pressure. This will tend to result in potentially important relationships getting lost in both case-control and cohort epidemiology studies, particularly where the analyses are attempting to dissect out the contributions of factors which are already closely correlated and therefore easily confused.

This methodological problem is further worsened by limited information on which aspects of the OSAHS might be the important drivers of adverse vascular risk (particularly blood pressure). Academic attention tends to focus on the number or severity of the nocturnal respiratory events, presumably because this is relatively easily measured. In reality, any number of other factors such as hormonal disturbances, behaviour changes, or the intensity of daytime sleepiness might be the salient factors and these are certain to have weak and probably non-linear relationships with simple indices of breathing disturbance.

These methodological debates inevitably seem rather academic and dry, but the distortion they can produce in data collected with care and with the best of intentions can be very important. Here, the importance of vitamin E in vascular risk provides a salutary lesson. Lower cardiovascular risk is strongly and independently associated with higher blood levels of vitamin E in very large observational studies (of over 50 000 subjects). However, when randomised trials of vitamin E supplementation aimed at reducing vascular risk are performed, the intervention is proved to be entirely without benefit.[16]

INTERVENTION TRIALS OF OSAHS TREATMENT AND BLOOD PRESSURE

As the vitamin E and cardiovascular risk story emphasises, the randomised clinical trial presents the opportunity to assess properly whether correcting a physiological disturbance produces the expected (and desired) outcome. Of course, a negative trial result does not exclude an aetiological relationship between a physiological disturbance and a consequence but, provided the trial is adequately powered, it does show that the treatment is ineffective for that outcome. There are now six randomised controlled trials examining the effect of nasal continuous positive airway pressure (nCPAP) treatment for OSAHS on systemic arterial blood pressure, and these are summarised in table 2. These trials should provide sound primary data for discussion in this area.

Superficially there is a conflict between these trials with some being clearly positive, suggesting nCPAP reduces blood pressure in OSAHS, and some negative. However, a detailed examination of the data may provide an explanation for this

Table 2 Randomised controlled studies of blood pressure and OSAHS

Study	No of subjects	Epworth Sleepiness Score	AHI	Placebo	Outcome	Comments
Faccenda[17]	68	Mean 15	Mean 35	Placebo tablet	1.5 mm Hg diastolic BP fall with CPAP	Subgroup analysis showed greatest BP fall in those with most severe disease (RDI >20)
Dimsdale[20]	39	Not documented	Mean RDI 48.1	Sham CPAP	About 5 mm Hg mean nocturnal BP fall	One week treatment; fall in daytime BP in placebo group at 1 week
Barbe[18]	55	Mean 7	Mean 56	Sham CPAP	No change in BP	Patients with no hypersomnolence compared with other RCTs
Pepperell[1]	95	Mean 16	Mean 4% dip rate 37	Sham CPAP	Mean BP fall 3.3 mm Hg	Subgroup analysis showed greatest BP fall in those on antihypertensives
Monasterio[22]	125	Mean 12.6	Mean 20	Conservative treatment	No change in BP at 3 and 6 months	No BP effect in patients with mild disease
Becker[19]	32	Mean 14	Mean 64	Partially therapeutic sham CPAP	Mean BP fall 9.9 mm Hg	9 weeks of treatment, more severe disease, two-thirds on antihypertensives

AHI, apnoea/hypopnoea index; BP, blood pressure; CPAP, continuous positive airway pressure; RDI, respiratory disturbance index; RCT, randomised controlled trial.

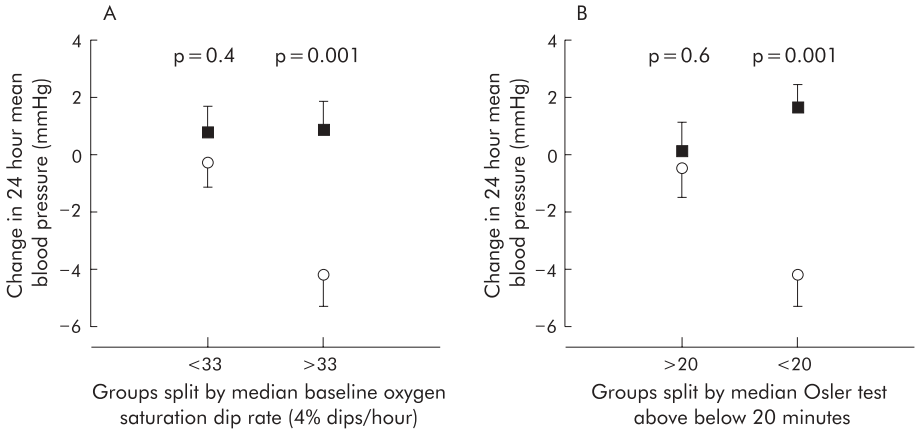

Figure 1 Fall in blood pressure with therapeutic nasal CPAP in the Oxford randomised placebo controlled study.[1] A greater fall in 24 hour mean blood pressure was seen in subjects with a baseline 4% oxygen desaturation dip rate of >33 (A) and in those with <20 minutes awake on the baseline Osler test (B).

disparity and perhaps also indicate which subgroups of patients with OSAHS might benefit from nCPAP therapy in terms of blood pressure control.

The first study published was a crossover trial of nCPAP versus an oral placebo from the Edinburgh group.[17] Overall, this study showed a just detectable fall in blood pressure in 68 patients with, on average, moderately severe OSAHS (AHI 35/hour, Epworth sleepiness score 15). Interestingly, on a post hoc analysis this benefit occurred in the 14 subjects with more severe disease (>4% desaturation rate of >20 per hour).

The Spanish collaborative study[18] was negative. In this study 55 subjects were randomised in a parallel trial to therapeutic nCPAP or subtherapeutic nCPAP (control group). Intentionally, this group studied patients with mild/moderate obstructive apnoea on respiratory criteria with little daytime sleepiness (>4% desaturation rate >30 per hour, Epworth score <11).

The Oxford study also used a parallel subtherapeutic controlled model[1] but in patients with quite severe disease, having both sleepiness and marked hypoxaemia (mean >4% desaturation rate 37 per hour, mean Epworth sleepiness score 16). Overall, this study showed a significant therapeutic blood pressure response to treatment and, again, post hoc subgroup analysis showed that this was mostly limited to patients with the most severe disease (>4% desaturation rate >33 per hour). In this subgroup the fall in blood pressure was enough to reduce the theoretical risk of stroke by about 35%.

In this study there was also a relationship between the severity of the patients' Osler (Oxford Sleep Resistance) test (a modified maintenance of wakefulness test), measured sleepiness, and the magnitude of their blood pressure fall with nCPAP.[1] As shown in fig 1, this was just as powerful a predictor of the fall in blood pressure with nCPAP as was the severity of the respiratory disturbance. The change in 24 hour mean blood pressure with therapeutic nCPAP treatment is shown, with the groups split into those with a baseline 4% oxygen desaturation dip rate above or below 33 (the median dip rate) in fig 1A and with the groups split by baseline Osler test result of more or less than 20 minutes in fig 1B. The therapeutic blood pressure fall is as strongly correlated with sleepiness as it is with objective sleep apnoea severity. This shows the apparent limitation of the therapeutic benefit of nCPAP to sleepy patients with typical OSAHS, which is consistent with the collaborative Spanish study.[18] Interestingly, we found that this relationship appeared partially independent of objective OSAHS severity, suggesting perhaps that the mechanisms causing the sleepiness are themselves the cause of some of the blood pressure fall with nCPAP.[1]

In a recently published study by Becker *et al*,[19] patients were randomised to receive fully therapeutic or partially therapeutic nCPAP (which reduced apnoeas by up to 50%). The large fall in day and night blood pressure seen in the therapeutic group (about 10 mm Hg) may be partly explained by the inpatient (and therefore minimally ambulant) hospital setting of the study, the severity of OSAHS studied (mean apnoea hypopnoea index 64), the longer length of CPAP treatment (9 weeks compared with 4 weeks in the Edinburgh and Oxford studies), and the fact that two thirds of those completing the study were on antihypertensive medication. In the Oxford study, antihypertensive medication also seemed to predict a large therapeutic response.[1] Of interest in the study by Becker *et al* is the fact that no blood pressure reduction was seen in the partially treated group (the control arm) despite a reduction in AHI of up to 50%, demonstrating the importance of complete resolution of OSAHS.

The San Diego study[20] showed a fall in daytime blood pressure and a lesser effect on night time blood pressure of a magnitude similar to that seen in the Oxford study. They studied a small population over 10 days, also demonstrating a reduction in daytime plasma norepinephrine levels and night time urinary norepinephrine excretion.[21] A small reduction in blood pressure was also seen in the placebo CPAP group.

The randomised trial by Monasterio *et al*[22] did not use a control intervention (nCPAP is compared with conservative care) and quantified blood pressure from office cuff recordings. These results are therefore difficult to compare directly with the other trials using more rigorous assessment methods.

In summary, these trials all show convincing falls in blood pressure in sleepy patients with severe OSAHS, and the magnitude of this benefit seems largest in patients with OSAHS which is severe on both objective (sleep study) and subjective (sleepiness) criteria and in those patients with treated hypertension at baseline. There is no benefit in subjects without daytime sleepiness.

CONFLICTS BETWEEN CLINICAL TRIAL DATA AND NON-INTERVENTIONAL DATA

There is an obvious and interesting apparent discrepancy between the interventional data discussed above and the

observational epidemiology and case-control studies. Specifically, ''mild'' OSAHS (defined as having minimal symptoms and/or few respiratory events) does not appear to be associated with substantial therapeutic blood pressure falls following nCPAP, but is apparently independently associated with raised blood pressure in the community.

There are two likely explanations for this apparent dichotomy. Firstly, it is possible that the clinical trial data are simply underpowered to detect the therapeutic benefit in patients with mild disease. Secondly, it is possible that two separate mechanisms are present to explain the data—one responsive to nCPAP and present in subjects with severe disease and one unresponsive to nCPAP (and perhaps methodological in nature) seen in the community epidemiology studies. This is not impossible, given the plethora of potential explanations for the community data explored in the section discussing the interpretation of non-interventional trial data (above). There are as yet very few data in subjects with mild disease and specific sizeable trials are needed in this area to answer this important question.

CONCLUSION

Robust clinical trial data now show that OSAHS is independently associated with systemic hypertension and that blood pressure falls when severe sleep apnoea is treated with the most effective available therapy, nasal CPAP. There remains a conflict between the apparent size of the effect seen in mild disease in observational studies compared with the small or absent effect in the intervention trials. This may simply be due to the lack of adequately powered trials or to methodological problems with the observational data. Large intervention trials will resolve this question in due course. For the clinician, the current message is that treating a typical patient with severe OSAHS (for which the majority of nasal CPAP therapy is prescribed) produces clinically useful blood pressure reductions as well as yielding important symptomatic benefits.

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