ORIGINAL ARTICLE

Hypertension and catecholamine levels in sleep apnoea

Col Vasu Vardhan*, Col K Shanmuganandan†

ABSTRACT

BACKGROUND

Sleep-disordered breathing has been strongly associated with systemic hypertension. Increased sympathetic activity in sleep-disordered breathing may be responsible for this association.

METHOD

In this sleep clinic-based study, 82 newly diagnosed patients of sleep-disordered breathing were evaluated for hypertension, and their plasma and urinary levels of catecholamines were measured. Catecholamine levels were then compared separately with the severity of sleep apnoea and blood pressure (BP).

RESULTS

The prevalence of hypertension in the study population was 46.3%. The BP showed a strong and statistically significant correlation with apnoea-hypopnoea index (diastolic, $r=0.65$, $P<0.001$ and systolic, $r=0.60$, $P<0.001$) which was maintained even after the results were analysed separately for obese and non-obese subjects. Both plasma and urinary levels of catecholamines were greater in patients with severe sleep apnoea (compared to nonsevere cases) and in those with hypertension compared to normotensives. However, statistical significance was achieved only for urine catecholamines and not for plasma catecholamines in both the cases.

CONCLUSION

Hypertension is highly prevalent among Indian subjects with obstructive sleep apnoea. Catecholamine levels are significantly higher in hypertensive than in normotensive apnoeics and are also directly related to the severity of obstructive sleep apnoea. Twenty-four hour urinary catecholamine levels are more valid measures of sympathetic activity than spot plasma samples.

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Key Words: catecholamines; hypertension; sleep apnoea; sleep-disordered breathing; sympathetic

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INTRODUCTION

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease. About 50% of obstructive sleep apnoea (OSA) patients are hypertensive,[1] and an estimated 30% of hypertensive patients also have OSA, often undiagnosed.[2–4] Nocturnal sympathetic activation and consequent higher sleep-related blood pressure (BP) may attenuate the nocturnal dipping of BP.[5] Increased sympathetic activity has been widely demonstrated in patients with OSA[6–9] and has been considered as the main link in the possible cause–effect relationship between OSA and hypertension.[7,10,11] Moreover, this altered sympathetic activity has been demonstrated to be corrected by continuous positive airway pressure treatment.[12,13] The aim of the present study is to estimate the prevalence of hypertension in patients with sleep-disordered breathing (SDB) in an Indian population, estimate the sympathetic activity in these patients as assessed by blood catecholamine levels, and assess the correlation between the catecholamine levels and BP in these patients.

MATERIALS AND METHOD

Population

The study was carried out on 82 patients suffering from SDB which was diagnosed on the basis of polysomnography (PSG) done on patients reporting at medical outpatient department at AFMC, Pune, with either history suggestive of SDB or referred for PSG from other departments.

Study Design

All suspected cases of SDB were subjected to a whole night attended PSG in the sleep lab. Thirty-two channels polysomnograph (Recorder and Medicare Systems Pvt Ltd, India) was used for this purpose. The PSG consisted of continuous polygraphic recording from surface leads for electroencephalography, electro-oculography, electromyography, electrocardiogram, pressure transducers for nasal airflow, thoracic, and abdominal impedance belts for respiratory effort, pulse oximetry for oxyhaemoglobin level, microphone for snoring, and sensors for leg and sleep position. Sleep data was scored according to the latest American Association of Sleep Medicine (AASM) criteria.[14] The average number of episodes of apnoea and hypopnoea per hour of sleep (the apnoea-hypopnoea index [AHI]) were calculated as the summary measurement of SDB. Respiratory effort related arousal (RERA) was defined as flattening in the airflow

signal >10 seconds followed by an arousal and an abrupt reversal in flow to a round shape, that does not qualify as hypopnoea. Respiratory effort related arousal index was defined as RERA events per hour of sleep. Respiratory-disturbance index (RDI) was defined as AHI+RERA Index. Measures of body habitus were recorded by standard anthropometric methods. Patients with an AHI >5 or RDI >10 were taken up for further analysis.

Blood pressure was checked in the morning after PSG. Included patients were interviewed for history of hypertension and any other known illness. Subjects were asked about the duration of their diagnosis of hypertension, how long they had been treated with anti-hypertensive drug(s), and which drug(s) they were receiving. Sitting BP was measured by a nurse in the morning after the night recording and thereafter once a week for three weeks. Informed consent was taken. Tapering of anti-hypertensives was done for patients already on anti-hypertensives. Patients with systolic pressure over 180 mmHg or diastolic pressure over 110 mmHg anytime during the three weeks were excluded from the study. The subjects were considered to be hypertensive if they had been receiving anti-hypertensive medication or if they satisfied the Joint National Committee seven criteria for hypertension.[15] Patients with age <16 years, insomnia or secondary hypertension were excluded from the study.

At the end of three weeks patients were called back and morning resting blood sample as well as 24-hour urine sample was collected for catecholamine estimation.

Statistical Analysis

Data were collected on a predesigned printed format. Statistical analysis was performed using a statistical software package (Epi info 8, version 3.2.1). All continuous variables were summarised in terms of mean (SD), and categorical variables were expressed as percentages. Comparison between groups was performed with the student *t*-test for continuous variables and the Pearson χ^2-test for discrete variables. Linear correlation was applied for continuous variables for comparison. All significance tests were two-sided, and a *P* value of <0.05 was considered to be statistically significant.

RESULTS

The recruitment of cases was done over two years from February 2008. Ninety-six patients were detected to have PSG evidence of SDB and among these, 90 patients met the criteria for inclusion in the study but five patients did not give consent for further study. Thus, 85 patients were taken up for study. Out of these three patients did not complete the study and finally 82 patients were taken up for analysis of the results. Table 1 shows the characteristics of the study population.

The mean age of the population was 55.22 years (±9.17). The youngest patient was 36-year-old and the oldest was 70-year-old. Mean body mass index (BMI) was 31.57 Kg/m^2 (±4.49). Fourteen patients were already known cases of hypertension on anti-hypertensive medication. Six patients gave history of having been detected to have high BP in the past but were not on any treatment or had been advised salt restriction and regular monitoring. Nine patients were known cases of diabetes mellitus and four were on treatment for coronary artery disease. There were also four patients with known dyslipidaemia and three patients with bronchial asthma. However, since this was a clinic-based study, an over representation due to referral-bias has to be kept in mind. None of these patients were already known cases of SDB.

Table 1 Characteristics of the population.

Variables	*n* (%)
Males	64 (78)
Females	18 (22)
Age	55.22 (±9.17)
Weight	89.21 (±11.41)
BMI (Kg/m^2)	
<25	5 (6.1)
≥25 & <30	30 (36.6)
≥30 & <35	31 (37.8)
≥35 & <40	11 (13.4)
≥40	5 (6.1)
Hypertension	38 (46.3)
Systolic BP ≥140	32 (39)
Diastolic BP ≥90	35 (42.7)
AHI >30	42 (51.2)

AHI: apnoea-hypopnoea index, BMI: body mass index, BP: blood pressure.
Data are presented as mean±standard deviation (SD) or *n* (%).

Eleven (13.41%), 29 (35.37%) and 42 (51.22%) subjects, respectively, had mild, moderate, and severe SDB. The mean AHI was 56.28/hour (±40.31). Respiratory-disturbance index was found to have absolute linearity with the AHI with a correlation coefficient of 0.999, and was thus not separately assessed in further analysis. The severity of disease was defined by AHI. The highest AHI found was 128.02/hour with a corresponding RDI of 135.97/hour in a patient with metabolic syndrome (obesity, hypertriglyceridemia, diabetes, and hypertension).

Blood Pressure and Severity of Sleep Apnoea

Thirty-eight (46.3%) subjects had hypertension (according to JNC-7 criteria). Fourteen of these patients were already on anti-hypertensive medication. Three patients had isolated systolic hypertension and six patients had isolated diastolic hypertension. Table 2 shows the association between AHI and BP. A statistically significant association existed between BP and AHI. To eliminate the confounding due to obesity, the association was assessed separately for patients with BMI <30 Kg/m^2 and those with BMI ≥30 Kg/m^2. Fisher exact test was used and the association maintained its statistical significance (*P* <0.05) for both the groups.

Pearson's linear regression was applied to assess the relationship of systolic and diastolic BP with BMI and AHI. Both

Table 2 Blood pressure and severity of sleep apnoea.

	AHI > 30	AHI ≤ 30	Significance
All patients (n=82)			
No. of subjects	42	40	
No. of hypertensives	32 (76.2%)	6 (15%)	P<0.05
BMI <30 (n=35)			
No. of subjects	7	28	
No. of hypertensives	4 (57.1%)	3 (10.7%)	P<0.05
BMI ≥30 (n=47)			
No. of subjects	35	12	
No. of hypertensives	28 (80%)	3 (25%)	P<0.05

AHI: apnoea-hypopnoea index, BMI: body mass index.
Data are presented as n (%).

diastolic (r=0.65, P <0.001) and systolic (r=0.60, P <0.001) pressures had a stronger co-relation with AHI levels than BMI (r=0.58 for both, P <0.001).

Catecholamines

Plasma and urine levels of epinephrine and norepinephrine were assessed for all patients. All patients with catecholamine levels beyond the normal range described were evaluated in detail to rule out other causes like pheochromocytoma with the help of clinical profile, catecholamine patterns, and imaging. No such causes were found in any patient. One patient had an outrageously high plasma norepinephrine levels (733.3 pg/mL). After ruling out pheochromocytoma, it was attributed to anxiety, pain due to venepuncture, or possibly due to lab error. Mean plasma norepinephrine levels with inclusion and exclusion of that value were 159.89 (±75.89) pg/mL and 152.81 (±40.86) pg/mL, respectively. Mean plasma epinephrine, urinary norepinephrine and urinary epinephrine values were 47.81 pg/mL, 55.11 µg/day and 8.22 µg/day, respectively. All the catecholamine measures were higher in those with higher AHI levels compared to those with AHI <30/hour (Table 3) and in hypertensive patients compared to normotensive patients (Table 4). However, statistical significance was achieved only for urine catecholamine levels in both the cases and not for plasma levels of catecholamines.

To assess the significance of association between urine and plasma catecholamine levels and hypertension, 'unpaired t-test (unequal variance)' was applied and again, a statistically significant association was seen only with urine catecholamine levels and not with plasma catecholamine levels (P <0.01).

Pearson's linear regression was applied to assess the co-relation between the plasma and urine catecholamine levels with systolic and diastolic BP, AHI levels, and BMI (Table 5). Again, a statistically significant, moderate to good co-relation was achieved for urinary catecholamine levels with BP (both systolic and diastolic), AHI, and BMI but not for plasma catecholamine levels. The co-relation was stronger with BP than other variables.

Considering the moderate co-relation between catecholamine levels and BMI, the urine catecholamines for hypertensives and normotensives were tabulated separately for obese and non-obese patients, to eliminate the effect of obesity as a potential confounding factor. The mean catecholamine levels (both epinephrine and norepinephrine) were higher in patients with hypertension compared to normotensives for both the patient groups (Table 6).

Table 3 Distribution of catecholamine levels according to severity of sleep apnoea.

Catecholamine levels	AHI > 30 (42)	AHI ≤ 30 (40)	P value
UE (µg/d)	11.17 (±10.43)	5.13 (±3.87)	<0.001
UNE (µg/d)	79.15 (±66.89)	29.85 (±26.38)	<0.001
PE (pg/mL)	51.44 (±44.49)	43.98 (±26.78)	>0.05
PNE (pg/mL)	168.93 (±99.23)	150.39 (±37.77)	>0.05

AHI: apnoea-hypopnoea index, PE: plasma epinephrine, PNE: plasma norepinephrine, UE: urine epinephrine, UNE: urine norepinephrine.
Data are presented as mean (±standard deviation [SD]).

Table 4 Distribution of catecholamines according to the blood pressure levels.

Catecholamine levels	Hypertensives (38)	Normotensives (44)	P value
UE (µg/d)	12.82 (±10.41)	4.25 (±2.58)	<0.001
UNE (µg/d)	93.23 (±63.52)	22.17 (±13.76)	<0.001
PE (pg/mL)	51.41 (±45.82)	44.70 (±27.14)	>0.05
PNE (pg/mL)	172.24 (±104.29)	149.23 (±35.18)	>0.05

PE: plasma epinephrine, PNE: plasma norepinephrine, UE: urine epinephrine, UNE: urine norepinephrine.
Data are presented as mean (±standard deviation [SD]).

Table 5 Pearson co-relation of catecholamines with blood pressure, body mass index and apnoea-hypopnoea index.

	Diastolic pressure	Systolic pressure	AHI	BMI
PE	0.282*	0.234*	0.166	0.243*
PNE	0.244*	0.231*	0.188	0.119
UE	0.609**	0.556**	0.458**	0.458**
UNE	0.750**	0.758**	0.514**	0.513**

AHI: apnoea-hypopnoea index, BMI: body mass index, PE: plasma epinephrine, PNE: plasma norepinephrine, UE: urine epinephrine, UNE: urine norepinephrine.
*Correlation significant at the 0.05 level (2-tailed).
**Correlation significant at the 0.01 level (2-tailed).

DISCUSSION

Being a clinic-based study, study population was expected to comprise of patients with more severe disease as compared to studies that have been conducted on population-based samples.[16–18] Prevalence of hypertension (by the JNC-7 criteria) in newly

Table 6 Distribution of catecholamines according to the blood pressure levels and body mass index.

		Hypertensives	Normotensives	*P* value
BMI < 30	Number of subjects	*n* = 7	*n* = 28	
	UE (μg/d)	8.46 (± 2.83)	3.61 (± 2.01)	< 0.05
	UNE (μg/d)	58.23 (± 28.65)	18.78 (± 11.20)	< 0.05
BMI ≥ 30	Number of subjects	*n* = 31	*n* = 16	
	UE (μg/d)	13.80 (± 11.26)	28.13 (± 16.06)	< 0.05
	UNE (μg/d)	101.14 (± 66.80)	5.37 (± 3.11)	< 0.05

BMI: body mass index, UE: urine epinephrine, UNE: urine norepinephrine.
Data are presented as mean (± standard deviation [SD]).

diagnosed sleep apnoea patients was 46.3%. This is in line with the results of other clinic-based studies.[19–21]

Our results point towards a significant association between BP and sleep apnoea and the relationship is probably causative rather than an incidental one. The diastolic pressure seems to be affected more than systolic pressure as also shown in some other studies.[22–24] Not many studies on Indian population are available on the subject. Udwadia and colleagues demonstrated in their study that although an association of SDB with hypertension was significant, multiple logistic regression analysis did not select hypertension as a principle covariate.[25] However, a high prevalence of hypertension in sleep apnoea has been unequivocally demonstrated in the present study as well as other studies[19–21] and emphasises the role of early diagnosis and treatment of sleep apnoea patients as well as the importance of evaluating all the newly diagnosed sleep apnoeic patients for hypertension.

The analysis of catecholamine levels in severe and nonsevere sleep apnoea patients revealed that both plasma and urinary levels of epinephrine (E) and norepinephrine (NE) were greater in patients with AHI >30 compared to those with AHI ≤30. However, statistical significance was achieved only for urine catecholamines and not for plasma catecholamines. Similarly the mean catecholamine levels were higher in patients with hypertension compared to normotensive patients but again, the statistical significance was achieved only for urinary levels of catecholamines and not for plasma catecholamines.

Linear regression showed moderate to good co-relation between urinary catecholamine levels and both diastolic and systolic pressures. These results point towards a possible role of raised catecholamine levels in patients of sleep apnoea in causation or aggravation of hypertension. Catecholamine levels are higher in patients with more severe sleep apnoea and the same patients also appear to have higher BP.

Both NE and E can rapidly affect BP, but their effects and their origin differ.[26] Norepinephrine induces a generalised vasoconstriction and an increase in both systolic and diastolic BP. It is both a hormone secreted by the adrenal medulla and the postganglionic sympathetic nervous system mediator. Norepinephrine released at the synaptic level reaches to some extent the bloodstream, so that plasma NE is believed to reflect sympathetic nervous system activity. Epinephrine increases cardiac output and systolic BP. It is only released in the bloodstream by the adrenal medulla. Since both NE and E are excreted with urine, either after metabolisation or unmodified, it is possible to derive indications on sympathetic nervous system and adrenal medulla activity by measuring urinary catecholamine excretion. Although catecholamines are mostly excreted in urine as their metabolites, the small urinary quantities of unmodified NE and E are believed to closely reflect the total release of catecholamines. Urinary measurements may reflect more closely the average level of catecholamine release during prolonged periods compared to plasma levels.

The persistent elevation of NE levels in OSA suggests that sympathetic activity in this syndrome is constantly elevated. A similar conclusion was also reached by Hedner and colleagues.[8] Marrone and colleagues showed in their study that OSA was associated with a steadily increased sympathetic tone in 24 hours, even when patients were normotensive during wakefulness.[26] However, there have been disparate results in the existing literature as regards to the predominant catecholamine responsible for the increased sympathetic activity in sleep apnoea.[9] Increases in NE have more frequently been reported among sleep apnoeics, than increases in E. This supports the finding that release of NE is mainly a consequence of physiological stress, while the release of E is associated with psychological stress. Moreover, sleep apnoea may excite sympathetic nerves more so than cause adrenomedullary response. In our study, however, both the catecholamines were raised and had moderate to good co-relation with the severity of sleep apnoea.

Unlike many past studies,[9] we took precautions to control for the effects of anti-hypertensive medication on the catecholamine levels, by obtaining the samples after 3-week tapering of the medications.

The effect of body weight on sympathetic activity is controversial.[26] However, since obstructive sleep apnoea syndrome (OSAS) is common in obese subjects, it would be hypothesised that the reported increase in sympathetic activity in obese subjects, when present, was related at least in part to undiagnosed OSAS. In fact, in one study in which obese subjects with and without OSAS were compared, the OSAS subjects showed a higher NE excretion, suggesting a possible additive effect of obesity and OSAS on catecholamine release.[27] We compared the

urinary catecholamine levels in hypertensives and normotensives for both obese and non-obese population and found higher urinary epinephrine and norepinephrine levels in hypertensives in both the patient groups ($P<0.05$).

We did not get statistically significant results with the plasma catecholamine levels, unlike the urine catecholamine levels. Several reasons could have been responsible for this. The sampling and storage procedures for plasma catecholamines require considerable care in order to attain meaningful values.[28] In addition, plasma NE levels are influenced by peripheral mechanisms such as changes in re-uptake/release, metabolic degradation, diffusion, and regional and local circulation.[29] Venepuncture can itself cause a rise in catecholamine levels. Also, because of the rapid secretion, rapid variability, and brief half-life of catecholamines, 24-hour urinary sample, as done in our study, by virtue of their integration through 24 hours was probably a better and more valid indicator of the sympathetic activity than spot plasma samples. Use of multiple plasma samples obtained through an indwelling catheter, rather than venepuncture, would probably yield results paralleling those obtained from urinary samples. This issue warrants further studies for validation.

CONCLUSION

We conclude that hypertension is highly prevalent among Indian subjects with OSA. The severity of hypertension is directly related to the severity of OSA as measured by AHI. Both epinephrine and norepinephrine levels are significantly higher in hypertensive apnoeics than normotensive apnoeics. Levels of catecholamines are also directly related to the severity of apnoea. Thus increased sympathetic activity in OSA probably has an aetiological role in causation of hypertension in these patients. We also inferred that 24-hour urinary catecholamine levels are more valid measures of sympathetic activity than spot plasma samples.

Intellectual Contributions of Authors

Study concept: Col Vasu Vardhan, Col K Shanmugandan
Drafting and statistical analysis: Col Vasu Vardhan, Col K Shanmugandan
Manuscript revision: Col Vasu Vardhan, Col K Shanmugandan
Study supervision: Col Vasu Vardhan, Col K Shanmugandan

CONFLICTS OF INTEREST

None identified.

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Journal scan

Watters JM, Van PY, Hamilton GJ, Sambasivan C, Differding JA, Schreiber MA. Advanced hemostatic dressings are not superior to gauze for care under fire scenarios. J Trauma 2011;70:1413–1419.

The advanced haemostatic dressings perform superior to standard gauze (SG) in animal haemorrhage models but require 2–5 minutes application time, which is not feasible on the battlefield. The authors from the Division of Trauma, Critical Care, and Acute Care Surgery, Department of Surgery, Oregon Health & Science University, Portland, Oregon carried out a clinical study on animals. Twenty-four swine received a femoral artery injury, 30 seconds uncontrolled haemorrhage and randomisation to packing with SG, combat gauze (CG), or celox gauze (XG) without external pressure. Animals were resuscitated to baseline mean arterial pressures with lactated ringers and monitored for 120 minutes. Physiological and coagulation parameters were collected throughout. Dressing failure was defined as overt bleeding outside the wound cavity. Tissues were collected for histological and ultrastructural studies. All animals survived till study end. There were no differences in baseline physiological or coagulation parameters or in dressing success rate (SG: 8/8, CG: 4/8, XG: 6/8) or blood loss between groups (SG: 260 mL, CG: 374 mL, XG: 204 mL; $P>0.3$). Standard gauze (40±0.9 seconds) packed significantly faster than either the CG (52±2.0) or XG (59±1.9). At 120 minutes, all groups had a significantly shorter time to clot formation compared with baseline ($P<0.01$). At 30 minutes, the XG animals had shorter time to clot compared with SG and CG animals ($P<0.05$). All histology sections had mild intimal and medial oedema. No inflammation, necrosis, or deposition of dressing particles in vessel walls was observed. No histological or ultrastructural differences were found between the study dressings. The authors concluded that advanced haemostatic dressings do not perform better than conventional gauze in an injury and application model similar to a care under fire scenario.

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