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Early View

Original article

Non-dipping nocturnal blood pressure correlates with obstructive sleep apnoea severity in normotensive subjects and may reverse with therapy

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Please cite this article as: Crinion SJ, Kleinerova J, Kent B, *et al*. Non-dipping nocturnal blood pressure correlates with obstructive sleep apnoea severity in normotensive subjects and may reverse with therapy. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00338-2021).

Non-dipping nocturnal blood pressure correlates with obstructive sleep apnoea severity in normotensive subjects and may reverse with therapy.

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Introduction

Obstructive sleep apnoea (OSA) is highly prevalent in the general population with an estimated global prevalence of close to one billion affected (1). Hypertension is present in up to 50% of patients with OSA, which is about double the prevalence of hypertension in general population studies (2). A non-dipping nocturnal BP profile (< 10% day-to-night systolic blood pressure difference) is especially likely in OSA patients (3) (4) (5) (6), even in the absence of significant hypertension. The likelihood of non-dipping BP correlates with OSA severity in population studies (7) and cardiovascular events are more frequent in OSA patients with a non-dipping BP profile than those with a normal dipping pattern, even in the absence of diagnosed hypertension (8). Despite the extensive publications on the relationships between OSA and hypertension and responses to therapy, there are few data on the relationship between OSA and 24-hour BP patterns in OSA patients who are normotensive on 24-hour ambulatory BP monitoring (ABPM) and free of any cardiovascular disease or other chronic disorders. Sapina-Beltran and co-workers evaluated the impact of CPAP therapy on 24-hour BP levels in OSA patients who were normotensive on office BP measurements and demonstrated a significant difference in mean nocturnal BP between dipppers and nondippers after 6 months of CPAP therapy, the former showing an increase and the latter a decrease (9). The potential for BP reduction or return of a dipping pattern in normotensive patients with OSA would provide an additional consideration in treatment decisions for individual patients and may also have implications for the possible primary prevention of hypertension in such patients. The question of primary prevention assumes additional significance in the context of the recent SAVE trial which reported that CPAP therapy

conferred no benefit in the secondary prevention of cardiovascular morbidity and mortality in patients with pre-existing cardiovascular disease (10).

Based on these considerations, we studied the relationship between nocturnal blood pressure pattern and OSA in a prospective cohort of patients referred for investigation of suspected OSA who were proven normotensive on 24-hour ABPM and free of any cardiovascular or other comorbidity. The primary objective of the study was to examine the relationship of OSA with nocturnal BP dipping and other BP variables in such normotensive subjects. Secondary objectives were: (1) to explore a range of potential intermediate pathways in this relationship that have previously been associated with OSA, hypertension and other cardiovascular diseases; and (2) to assess the potential effects of therapy on nocturnal BP pattern in patients from the cohort who were diagnosed with OSA and commenced on CPAP therapy.

Methods

Subjects

Consecutive patients referred to the Sleep Clinic in St Vincent's University Hospital were screened for inclusion to the study and were considered if they were male and aged 18 to 70yrs without a known diagnosis of hypertension. Exclusion criteria included any previous investigation or diagnosis of obstructive sleep apnoea, history of cardiovascular disease (including hypertension, coronary artery disease, or previous myocardial infarction), metabolic disease (including diabetes), thyroid disease or any requirement for long term medication. Consenting participants were included if normotension was confirmed on ABPM. Prior approval was obtained from the Ethics and Medical Research

Committee of St Vincent's Healthcare Group, Dublin, Ireland and all subjects provided written informed consent.

Study Protocol

PSG

Subjects underwent an attended, inpatient polysomnography (PSG) in the Sleep Laboratory at St Vincent's University Hospital, Dublin, Ireland. Following the AASM 2012 (11) Scoring Manual, a ≥90% decrease in oronasal airflow below pre-event baseline for ≥10 seconds during sleep resulted in an apnoea, and a ≥30% decrease in oronasal airflow below pre-event baseline accompanied by either a ≥3% decrease in oxygen (O_2) saturations or an arousal from sleep resulted in the scoring of a hypopnoea.

ABPM

On the morning after PSG, an ambulatory blood pressure monitor (ABPM) was fitted to the subject's non-dominant arm (WatchBP03 (Microlife Corp., Taipei, Taiwan). The patient's self-reported routine sleep and wake times were programmed into the device and this information was rechecked with the patient when it was returned. BP measurements were taken every twenty minutes during daytime (awake) hours and thirty minutes during nighttime (asleep) hours to ensure at least one measurement per hour.

Biomarkers of intermediate pathways

Patients were instructed to void their bladder before getting into bed for the PSG. All urine voided throughout the night including the first void on waking in the morning was collected in a polyetheline container. 100mls 1M hydrochloric acid (HCl) was added to

the container prior to the collection as a preservative agent. Samples were analysed immediately after collection in the laboratory of St Vincent's University Hospital using high-performance liquid chromatography to determine urinary noradrenaline (nmol/L) for measurement of urinary catecholamines.

In the morning following the PSG, venous blood samples were taken from each patient in a fasting state using BD Vacutainers (Becton, Dickinson and Company, Franklin Lakes, USA). Two samples with added silica and one sample with added lithium heparin were centrifuged for 15 minutes at 1800rpm and 4°C to separate plasma and serum, respectively. Following centrifugation, the samples were separated into 0.5ml aliquots in sterile cryogenic vials and stored at -80°C for future analysis. After collection of all patient samples, analysis was done using commercially available sandwich Enzyme-Linked ImmunoSorbent Assays (ELISA) for the detection of plasma renin, interleukin-6 (IL-6), tumour necrosis factor alpha (TNFα), oxidised low-density lipoprotein (oxLDL) and endothelin 1.

CPAP

Subjects with OSA diagnosed on PSG were subsequently offered therapy with continuous positive airways pressure (CPAP) as per the departmental protocol, including attended inpatient CPAP initiation and titration. Subjects who accepted CPAP therapy were contacted and invited to return for repeat ABPM testing as per the protocol described above.

Statistical analysis

Data analysis was done using IBM SPSS Statistics for Windows (Version 20, Armonk, NY, USA). Patient characteristics and ABPM results were categorised into OSA severity quartiles based on the AHI. Data are displayed as mean (SD) or median (interquartile range) depending on distribution. Groups were compared by one-way ANOVA followed by Bonferroni post-hoc comparison. Patient characteristics were univariately correlated with % BP dip and non-dipping status. Linear and logistic regression models were built to calculate predictors of % BP dip and non-dipping status. Paired student T-test and McNemar's test were used to compare measured variables and ratio of non-dippers respectively in subjects' pre and post-CPAP therapy.

Results

Baseline characteristics

65 consecutive male patients were included in the study. Baseline characteristics of the study population, stratified by AHI quartiles, are described in table 1. The 4 groups were similar with regards to age, smoking status, lipid levels, renal function and Epworth sleepiness score. However, subjects with more severe OSA were more obese, had higher levels of glycosylated haemoglobin (HbA1c) and increased insulin resistance as calculated by HOMA-IR.

24-hour blood pressure recordings

Ambulatory blood pressure monitoring (ABPM) was obtained in all subjects. As shown in table 2, all subjects were normotensive and there was no difference in daytime values between AHI quartiles. However, nocturnal blood pressure increased with higher AHI and subjects in the 4^{th} AHI quartile had a significantly lower dipping ratio in comparison to subjects in quartile 1. Univariate linear correlation analysis showed a significant inverse correlation between the percentage in blood pressure dip and body mass index (BMI), neck circumference and markers indicating the severity of OSA. The presence of a non-dipping blood pressure status correlated with increasing AHI, oxygen desaturation index (ODI) and lower minimal oxygen saturation values (table 3). Stepwise multiple linear regression analysis identified the ODI and the amount of smoking (pack years) as independent predictors of blood pressure dip (table 4A). Furthermore, subjects in AHI quartile 4 versus quartile 1 had increased odds of a non-dipping blood pressure status, but this failed to reach statistical significance (p=0.063) (data not shown). However, increasing severity of ODI, but not AHI, conferred significantly increased odds of the non-dipping status, independent of age, BMI, smoking status and insulin sensitivity (table 4B).

Relationship between blood pressure dip and biomarkers of potential intermediate pathways

To gain insight into potential mechanistic pathways underlying the association of OSA and non-dipping blood pressure, we performed a correlation analysis of blood pressure values with markers of sympathetic activation, renin–angiotensin–aldosterone

system (RAAS) activity, oxidative stress, endothelial function and systemic inflammation. Only urinary norepinephrine as a marker of sympathetic activity correlated negatively with nocturnal systolic blood pressure and there was a trend towards significant correlation with the percentage of nocturnal dip (p=0.087) and non-dipping blood pressure status (p=0.058) (table 5).

Effect of CPAP therapy on blood pressure dip

Thirty one (n=31) in the cohort were commenced on CPAP therapy, of which twenty (n=20) agreed to return for repeat ABPM and assessment**.** The mean time on CPAP therapy at the return assessment was 18 months (+/-6). There was no change in BMI, no other diseases were diagnosed, or medications introduced. Objective CPAP compliance data was available in 19 of 20 subjects (95%), demonstrating a mean 90-day usage of 90.1% (+/-18.9) of nights. Mean usage hours per night over 90 days was 6.39 hours (+/-1.14). Average CPAP pressure was 10.7 cmH2O (+/-1.5). CPAP therapy resulted in significant improvement in nocturnal systolic blood pressure and blood pressure dip (figure 1A, 1B). Furthermore, the number of subjects with a dipping pattern increased from 5 (25%) to 9 (45%) (p=0.109).

Discussion

The principal finding of this study is that OSA correlates with loss of nocturnal BP dipping and other BP variables in this cohort of patients who had no comorbidity and were normotensive based on 24-hour ABPM measurements. The nocturnal dip in BP as well as the percent of non-dippers was more pronounced among the highest severity quartile of OSA and correlated strongly with the AHI and ODI. As a secondary end point,

the data suggest that effective therapy with CPAP in this normotensive cohort may be associated with significant recovery of the nocturnal BP dipping pattern in addition to a lowering of systolic BP levels.

Our findings agree with previous reports that a non-dipping nocturnal blood pressure (BP) profile is particularly likely in patients with OSA (12), even in the absence of significant hypertension (8). The prevalence of a non-dipping BP was higher in our cohort than that reported in other studies (7, 12). However, these latter cohorts included treated hypertensive subjects and thus represent more heterogeneous populations. Data from the Wisconsin Sleep Cohort Study indicate a dose-response increase in the development of non-dipping hypertension with severity of OSA at baseline when followed for 7 years (7), which is confirmed by the report of Seif and co-authors demonstrating that in patients with established cardiovascular disease and moderate or severe OSA there is a 4% increase in the odds of having a non-dipping BP profile per unit increase in AHI (5). Furthermore, recent evidence from this department indicates that non-dipping nocturnal blood pressure in hypertensive patients is a strong predictor of OSA, regardless of symptom profile (13).

The present data indicate that ODI was also an independent predictor of BP dip, consistent with previous research suggesting that measurements of oxygen desaturation, as a marker of OSA severity, are strongly associated with hypertension (14-16). Furthermore, stepwise linear regression analysis showed that ODI was superior to AHI in predicting nocturnal blood pressure dip (Table 4), which supports the previous report of Tkacova and co-authors that ODI is superior to AHI in the prediction of prevalent hypertension in a large sleep clinic population (15). Since ODI is the most relevant

clinical measure of intermittent hypoxia (IH), this finding supports IH as a key OSA-related variable that predicts loss of nocturnal dipping in OSA.

Effective therapy of OSA with continuous positive airway pressure (CPAP) has been demonstrated to lower blood pressure (4), especially at night (17), although the overall reduction in BP with CPAP therapy is relatively small (18) (19) (20) (21). 24-hour ambulatory blood pressure monitoring has been reported to be a useful tool in identifying diurnal BP patterns to help predict and quantify BP response to CPAP therapy in OSA (22). Although CPAP has been demonstrated to reduce the frequency of prehypertension or masked hypertension in patients with severe OSA (23), the ability of CPAP therapy in OSA patients to limit the future development of hypertension is not proven (24). The potential ability of CPAP therapy to reverse a non-dipping blood pressure in normotensive OSA and prevent future hypertension or cardiovascular events presents a possibility of primary prevention in this at-risk population.

Although only a secondary study end point, the present report demonstrating beneficial effects of CPAP on the nocturnal dipping BP profile in these normotensive OSA patients has implications for the future likelihood of cardiovascular morbidity in such patients. Sapina-Beltran and co-authors identified patients with normal office BP measurements and demonstrated a reduction in BP in after 6 months CPAP therapy (9). In this latter report, the benefits of CPAP therapy to BP variables principally related to nocturnal non-dippers and those with masked hypertension. Our study differed from this latter report in that no patient had masked hypertension as all subjects had normal 24-hour BP levels prior to enrolment. Another randomised study of CPAP therapy in severe OSA patients with pre-hypertension demonstrated a reduction in office systolic and

diastolic BP in treated patients compared to controls (25), and a recent meta-analysis confirms that elevated pre-CPAP BP values and age <60 years are factors more likely to predict a BP response in OSA (18). Male gender, Epworth sleepiness scale and BMI have been identified as predictors of BP reduction following CPAP therapy in normotensive OSA (26). Overall, our findings provide supportive evidence that CPAP therapy is beneficial in the primary prevention of hypertension in patients with OSA and are especially relevant in the context of the recent SAVE trial (10), which reported that CPAP was ineffective in the secondary prevention of cardiovascular morbidity and mortality among patients with established cardiovascular disease. Further controlled prospective studies of CPAP therapy in normotensive OSA populations will be required to confirm this potential benefit.

Potential intermediate mechanisms involved in the development of hypertension in OSA are likely multi-factorial, but sympathetic activation appears particularly important (4). Other proposed mechanisms include activation of the renin-angiotensin aldosterone system (RAAS) (27), systemic and vascular inflammation, oxidative stress, and endothelial dysfunction (28), although specific evidence relating these intermediate mechanisms to non-dipping nocturnal BP is limited (29). We evaluated a range of potential intermediate mechanisms in our study population but the only significant finding was a significant relationship between overnight urinary norepinephrine, which is a marker of sympathetic excitation, and nocturnal systolic BP levels. However, urinary norepinephrine showed only a non-significant trend towards a relationship with nocturnal BP dipping status. These findings agree with several previous reports indicating elevated urinary epinephrine levels and other measures of sympathetic

excitation in OSA (30, 31). No other significant relationship was found across the range of variables studied in our patient population and thus our data provide no further insight into the mechanisms of BP dipping in these subjects.

The present report has several important strengths. The study cohort represents a carefully selected consecutive group of patients referred for investigation of suspected OSA who were free of all other co-morbidities and were not taking any regular medication. All patients were normotensive based on 24-hr mean systolic and diastolic BP levels. These findings together with those of previous reports (32) suggest that large patient numbers may not be necessary to identify potential benefit of CPAP therapy for OSA in the primary prevention of hypertension.

The study also has several limitations. First, only male subjects were studied and thus the findings cannot be extrapolated to female OSA patients. This aspect is relevant in the context of recent reports indicating sex differences in clinical OSA phenotypes (33) and in predisposition to incident hypertension (34). Second, not all patients who were commenced on CPAP therapy for OSA returned for follow-up. This failure was despite repeated efforts by the lead investigator to contact these patients, some of whom could not be contacted, and others declined to repeat the initial protocol after a period on CPAP therapy. Thus, we cannot exclude the possibility of selection bias in those patients who returned for follow-up evaluation. Thirdly, the variables collected to represent intermediate mechanisms in the development of OSA were not repeated in the cohort of patients treated with CPAP, so no conclusions can be made as to whether CPAP affected these variables.

In conclusion, this report confirms the strong association in a normotensive cohort between OSA and nocturnal blood pressure and supports intermittent hypoxia as an important mechanistic pathway. These findings also provide supportive evidence that CPAP therapy may play a significant role in the primary prevention of hypertension in OSA patients, although further studies are required to confirm this possibility.

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Figure 1: A Nighttime systolic blood pressure (BP) and **B** Percent (%) of BP dip in a subset of subjects pre and post treatment with CPAP.

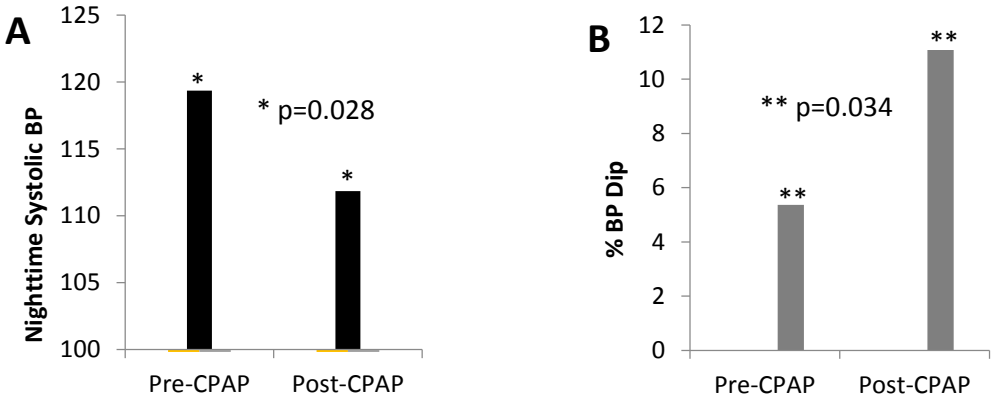

Table 1 Total cohort patient characteristics and blood pressure measurements stratified by OSA severity quartiles.

Patient Characteristics						
Variable	Total cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p value
n	65	16	17	16	16	
Age (years)	41 (7)	38 (6)	40 (8)	42 (8)	43 (7)	0.158
BMI (kg/m2)	33.5 (5.8)	30.1 (3.7)	30.9 (2.6)	34.8 (5.0)*	38.5 (6.9)*†	**<0.001**
Neck Circumference (cm)	43 (3)	41 (3)	43 (2)	44 (3)*	45 (3)*	**0.004**
Waist-Hip Ratio	1.00 (0.06)	0.98 (0.07)	1.00 (0.06)	1.00 (0.04)	1.04 (0.05)	0.115
Smoking (pack years)	9 (12)	9 (7)	8 (13)	13 (14)	7 (10)	0.566
Current smokers (%)	20%	25%	18%	25%	13%	0.862
Clinic systolic BP	137 (11)	136 (14)	136 (11)	140 (12)	138 (8)	0.706
Clinic diastolic BP	83 (8)	83 (9)	81 (7)	84 (9)	86 (7)	0.458
ESS score	11 (5)	10 (7)	12 (5)	12 (5)	12 (5)	0.885
HBA1c	37 (3)	36 (2)	35 (3)	36 (3)	39 (3)*†‡	**0.004**
HOMA	3.7 (2.9)	2.2 (1.1)	3.3 (1.9)	3.2 (1.9)	6.0 (4.1)*†‡	**0.001**
Total Cholesterol	4.9 (0.8)	5.1 (0.8)	4.8 (0.7)	5.0 (0.9)	4.8 (1.0)	0.652
Triglycerides	1.6 (0.8)	1.5 (0.9)	1.5 (0.7)	1.9 (1.0)	1.5 (0.8)	0.362
HDL	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	0.851
LDL	3.1 (0.7)	3.3 (0.6)	3.0 (0.7)	3.1 (0.7)	3.0 (0.9)	0.528
Creatinine	84 (12)	89 (14)	85 (14)	84 (11)	79 (8)	0.110
eGFR	97 (13)	95 (15)	97 (14)	96 (10)	102 (11)	0.400
AHI (events/hr)	13.6 (4.7-26.2)	1.3 (0.6-3.4)	7.7 (5.6-14.7)	19.7 (17.0-24.6)*	45.0 (33.5-75.6)*†‡	**<0.001**
ODI (events/hr)	12.2 (3.9-25.1)	1.8 (0.6-2.3)	6.4 (5.5-7.8)	17.2 (14.6-20.3)*	44.9 (26.6-62.5)*†‡	**<0.001**
TST90 (%)	0.6 (0.0-5.6)	0.0 (0-0.2)	0.1 (0-1.3)	2.2 (0.2-4.9)	19.8 (3.8-54.6)*†‡	**<0.001**
min SpO_2 (%)	87 (79-89)	89 (88-91)	88 (85-90)	83 (78-87)*	72 (67-84)*†‡	**<0.001**
Arousal Index (events/hr)	8.3 (5.2-16.4)	5.6 (3.8-7.1)	9.0 (5.6-14.7)	9.1 (4.5-12.7)	18.9 (7.0-31.7)*†‡	**0.001**

Values represent mean (SD) or median (interquartile range) depending on distribution. BMI: body mass index; ESS: Epworth Sleepiness Scale score; AHI: apnoea hypopnoea index; IQR: interquartile range; TST90: Total sleep time with O2 saturations <90%; BP: Blood pressure; HbA1c: glycosylated haemoglobin (mmol/mol).

* p<0.05 vs AHI quartile 1

† p<0.05 vs AHI quartile 2

‡ p<0.05 vs AHI quartile 3

Table 2 Total cohort blood pressure measurements stratified by OSA severity quartiles.

ABPM Results						
Variable	Total cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p value
ABPM day systolic	121 (9)	120 (9)	121 (9)	120 (9)	122(7)	0.851
ABPM day diastolic	74 (9)	73 (8)	74 (7)	71 (13)	77 (7)	0.355
ABPM night systolic	112 (10)	107 (10)	108 (9)	113 (9)	119 (7)*†	**0.001**
ABPM night diastolic	66 (8)	61 (9)	65 (8)	69 (9)	68 (6)	**0.039**
ABPM % dip	7.3 (7.7)	11.0 (6.0)	9.3 (7.2)	5.4 (9.2)	3.2 (5.9)*	**0.012**
% non-dippers	66%	56%	59%	63%	88%	0.216
% below daytime value of 135/85 mmHg	92%	94%	100%	88%	88%	0.464
%below nighttime value of 120/70 mmHg	69%	75%	77%	69%	56%	0.621

Values represent mean (SD) or percent of total. ABPM: Ambulatory blood pressure monitor.
* $p<0.05$ vs AHI quartile 1
† $p<0.05$ vs AHI quartile 2

Table 3 Univariate correlation of % blood pressure dip and non-dipping status with patient parameters.

	% Blood pressure dip		Non dipping status		
Variable	Correlation Coefficient	p value	B(95%CI)	Standardised Beta	p value
Age	-0.067	0.594	0.989 (0.923-1.060)	-0.11	0.759
BMI	**-0.248**	**0.022**	1.096 (0.987-1.218)	0.092	0.086
Neck circumference	-0.373	0.004	1.147 (0.952-1.383)	0.138	0.149
WHR	-0.168	0.258	1.223 (0.00-50465.75)	0.202	0.970
Smoking pack years	-0.238	0.061	0.975 (0.928-1.025)	-0.025	0.318
HbA1c	-0.192	0.125	1.139 (0.963-1.349)	0.131	0.129
HOMA	-0.227	0.087	1.170 (0.909-1.507)	0.157	0.223
Creatinine	-0.007	0.955	1.00 (0.959-1.043)	0.000	0.990
eGFR	0.047	0.710	1.001 (0.961-1.044)	0.001	0.951
Cholesterol	-0.019	0.881	1.238 (0.655-2.339)	0.213	0.511
Triglycerides	-0.183	0.144	1.831 (0.841-3.948)	0.605	0.127
HDL	0.151	0.229	0.423 (0.080-2.229)	-0.862	0.310
LDL	0.007	0.955	1.157 (0.560-2.390)	0.145	0.694
AHI	**-0.327**	**0.002**	**1.037 (1.000-1.075)**	**0.036**	**0.049**
ODI	**-0.371**	**0.002**	**1.042 (1.001-1.085)**	**0.041**	**0.044**
TST90	**-0.251**	**0.044**	1.126 (0.966-1.311)	0.118	0.128
Min O2 sats	**0.282**	**0.023**	**0.921 (0.850-0.998)**	**-0.082**	**0.045**
Arousal Index	-0.116	0.363	1.005 (0.961-1.052)	0.005	0.822

Table 4A Stepwise linear regression showing predictors of blood pressure dip (%), r square 0.235. **4B** Stepwise logistic regression showing predictors of a non-dipping status, r square 0.098.

	Variable	B(95%CI)	Standardised Beta	p value
A	ODI	-0.136 (-0.182- -0.09)	-0.351	**0.005**
	Smoking pack years	-0.216 (-0.131- -0.301)	-0.305	**0.014**
B	ODI	1.047 (1.001-1.095)	0.046	**0.045**

Independent variables AHI, ODI, age, BMI, smoking pack years, Min spO_2, HOMA. AHI: apnoea hypopnoea index; ODI: oxygen desaturation index; BMI: body mass index; ODI: oxygen desaturation index; Min spO2: minimum oxygen saturations; HOMA: Homeostasis model assessment.

Table 5 Univariate correlation of % blood pressure dip, nocturnal systolic blood pressure and non-dipping status with biomarkers of potential contributory pathways.

	% Blood pressure dip		**Nocturnal systolic blood pressure**		**Non dipping status**		
Variable	Correlation Coefficient	p value	Correlation Coefficient	p value	B(95%CI)	Standardised Beta	p value
Urinary norepinephrine	-0.242	0.087	**0.387**	**0.007**	1.006 (1.000-1.013)	0.006	0.058
Angiotensin II	0.078	0.539	-0.082	0.533	0.045 (0.00-1688.09)	-3.096	0.564
Renin	0.077	0.545	0.052	0.691	1.000 (0.999-1.000)	0.000	0.398
RHI	-0.100	0.482	-0.004	0.981	1.277 (0.425-3.544)	0.204	0.706
Endothelin 1	0.099	0.438	0.025	0.849	0.775 (0.584-1.027)	-0.255	0.076
CRP	-0.213	0.092	0.156	0.235	1.044 (0.898-1.214)	0.043	0.577
IL6	0.022	0.864	0.064	0.626	1.115 (0.906-1.374)	0.109	0.304
TNFa	0.147	0.248	-0.058	0.661	1.003 (0.939-1.072)	0.003	0.923