

## Research Paper

Diurnal changes in central blood pressure and pulse pressure amplification in patients with obstructive sleep apnoea<sup>☆</sup>

Yasmina Serinel<sup>a,b,c,\*</sup>, Camilla Hoyos<sup>a,d</sup>, Ahmad Qasem<sup>e</sup>, Brendon J. Yee<sup>a,b,f</sup>,  
Ronald R. Grunstein<sup>a,b,f</sup>, Keith H. Wong<sup>a,b,f</sup>, Craig L. Phillips<sup>a,b,g</sup>

<sup>a</sup> NHMRC Centre for Integrated Research and Understanding of Sleep (CIRUS), NHMRC Neurosleep Centre Woolcock Institute of Medical Research, The University of Sydney, NSW 2006, Australia

<sup>b</sup> The University of Sydney, Faculty of Medicine and Health, University of Sydney, NSW 2006, Australia

<sup>c</sup> Department of Respiratory and Sleep Medicine, Nepean Hospital, Derby St, Penrith NSW 2750, Australia

<sup>d</sup> School of Psychology, University of Sydney, Sydney, New South Wales, Australia

<sup>e</sup> Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, 2 Technology Place, NSW 2109 Australia

<sup>f</sup> Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Missenden Rd, Newtown NSW 2050, Australia

<sup>g</sup> Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, Reserve Rd, St Leonards, Sydney, NSW 2065, Australia

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## ABSTRACT

**Study objectives:** Recent evidence suggests that compared to peripheral blood pressure (BP), central BP may be more strongly associated with target organ damage and cardiovascular morbidity and mortality. Technological advances now allow the ambulatory measurement of peripheral and central BP over 24 h. For the first time, we set out to characterise the diurnal profile of central BP and pulse pressure amplification (PPA) in patients with obstructive sleep apnoea (OSA).

**Methods:** In this observational study, patients with moderate to severe OSA underwent 24 h central and peripheral BP testing before and after at least 4 weeks of CPAP therapy. Concurrent actigraphy was performed to confirm sleep and wake times.

**Results:** 36 patients were screened, 31 had successful testing (mean (SD) age  $45 \pm 10$  years, AHI  $58 \pm 27$  events/hr, Office BP  $136/89 \pm 10.7/9.5$  mmHg, 32% on anti-hypertensives, 77% dippers), 21 completed testing post CPAP. Central systolic and diastolic BP followed the same nocturnal dipping profile as peripheral BP, however the peripheral pulse pressure (PP) narrowed in sleep ( $-3.2$  mmHg,  $p < 0.001$ ), whereas the central PP remained unchanged ( $0.124$  mmHg, NS), causing a significant reduction in PPA overnight ( $-10.7\%$ ,  $p < 0.001$ ). The magnitude of dip in central systolic pressure was less than peripheral systolic pressure (by  $2.3$  mmHg,  $p < 0.001$ ). After treatment with CPAP, the PPA reduction overnight was attenuated (by  $-3.3\%$ ,  $p = 0.004$ ).

**Conclusions:** In moderate to severe OSA, central BP and PPA reduce overnight during sleep. Further randomised controlled studies are needed to quantify the differential effects of CPAP and anti-hypertensives on central versus peripheral BP.

## 1. Introduction

Obstructive sleep apnoea (OSA) is strongly associated with hypertension [1,2] and widely accepted as a risk factor for secondary hypertension [3,4]. Management of hypertension is more challenging in patients with OSA as evidenced by higher rates of refractory hypertension, greater nocturnal non-dipping [5–7], and sub-optimal responses to

anti-hypertensives.[8, 9] Furthermore, treatment of OSA with continuous positive airway pressure (CPAP) confers surprisingly modest benefits in terms of reducing blood pressure [10]. Hence, the mechanisms underpinning hypertension in OSA and how to best manage the condition in this vulnerable group are still poorly understood.

For decades, office peripheral (brachial) blood pressure (BP) as measured in a clinic setting has been used to determine future

<sup>☆</sup> This study was performed at the NHMRC Centre for Integrated Research and Understanding of Sleep (CIRUS), and NHMRC Neurosleep Centre Woolcock Institute of Medical Research, The University of Sydney, NSW 2006, Australia.

\* Corresponding author. Yasmina Serinel Woolcock Institute of Medical Research, 431 Glebe Point Rd, Glebe NSW 2037, Australia.

E-mail address: [Yasmina.serinel@sydney.edu.au](mailto:Yasmina.serinel@sydney.edu.au) (Y. Serinel).

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cardiovascular risk. However, 24 h ambulatory blood pressure monitoring (ABPM) has established itself as a superior predictor of cardiovascular mortality and morbidity [11, 12]. In particular, the ability to determine nocturnal blood pressure dipping status has greatly improved risk stratification [13]. Despite these advances, a major limitation of peripheral systolic BP is that it does not accurately represent central (aortic) systolic BP. This is because systemic arterial stiffness and its impact on wave reflection can vary both within individuals across time [14] and between individuals. This variation in arterial stiffness and in heart rate will directly alter the magnitude of the reflected component of the pulse pressure wave (augmentation pressure) which will in turn alter central aortic systolic pressure. Importantly, several studies have shown that static measurements of central BP have been associated with target-organ damage [15, 16] and cardiovascular risk, independent of peripheral BP [17, 18].

In this context, a key recent technological advancement has been the development of ambulatory BP devices that are able to capture not only inter-individual differences but also day-night changes in both peripheral and central (aortic) blood pressure [19]. By quantifying sleep aortic BP in particular this technology has the potential to greatly improve risk stratification. Furthermore, studies have shown that anti-hypertensive medications have differential effects on central aortic as opposed to peripheral BP which has significant therapeutic implications [20]. Additionally, the difference between central and peripheral blood pressure, known as pulse pressure amplification (PPA), is emerging as an important novel predictor of future cardiovascular events [21–23]. This new ambulatory technology therefore allows the examination of wake-sleep changes in PPA thereby providing further novel insights into arterial haemodynamics.

To date there have not been any published studies that have examined 24 h central blood pressure and PPA in patients with OSA. Additionally, there have been no studies of the diurnal properties of central BP in this population before and after treatment with CPAP. In this study, we sought to describe for the first time the diurnal nature of peripheral and central blood pressure and PPA over a 24 h period in patients with moderate to severe OSA. We also quantified in a smaller group, the relative wake-sleep changes in peripheral and central BP after treatment with CPAP therapy.

## 2. Methods

### 2.1. Study design

This was an observational study examining the diurnal profile of peripheral and central blood pressure and pulse pressure amplification in patients with OSA before and after CPAP therapy. The study protocol was approved by the NSW Sydney Local Health District Ethics committee (X15-0360 & HREC/15/RPAH/490). All patients signed a written informed consent.

### 2.2. Participants

Participants were recruited from a Sleep clinic (Woolcock Institute of Medical Research, Sydney, Australia) between September 2016 and October 2017. Male and female participants were eligible if they were aged 18 to 65yo, had moderate to severe untreated hypoxemic OSA (Apnoea-Hypopnea Index and Oxygen Desaturation Index-3%  $\geq 15$ /hr), and on fewer than three anti-hypertensive medications. Patient exclusion criteria were: severe hypertension (Office Systolic blood pressure  $\geq 180$  mmHg and/or Diastolic blood pressure  $\geq 110$  mmHg), severe OSA (minimum oxygen saturation  $\leq 65\%$  or Respiratory Disturbance Index  $> 80$ /hr) with excessive sleepiness at high risk of driving-related accidents, chronic kidney disease (eGFR  $< 60$ ) and uncontrolled medical problems.

All patients underwent gold standard overnight in-laboratory polysomnography to confirm OSA status and severity. Studies were scored according to the American Academy of Sleep Medicine criteria [24].

Once eligible, patients were fitted with the ambulatory blood pressure monitor and cuff (Oscar2 with SphygmoCor Inside, SunTech Medical, Model 250, NC, USA). The appropriate sized cuff was determined by measuring the patient's upper arm circumference. The device is a non-invasive oscillometric ambulatory blood pressure monitor and brachial cuff that is worn by the patient in the community. The machine was set to take readings every 30 min over a 24 h period. At these set intervals, the cuff inflates to obtain systolic and diastolic pressures based on pressure waves in the artery when occluded by pressure in the cuff (oscillometric method). The machine then deflates to 10 mmHg below diastolic pressure and captures volumetric waveforms. It then derives central arterial indices from the captured waveforms using a validated transfer function algorithm. As a peripheral BP device, the Oscar2 has met all requirements according to the International Protocol for the validation of blood pressure machines and the British Hypertension Society [25, 26]. The cuff-based measurement of brachial pressure waves in the Oscar2 and the transfer function for estimating central BP and augmentation index is identical to the SphygmoCor XCEL. This cuff-based technology has been compared against the gold standard non-invasive radial tonometry technology originally developed for SphygmoCor pulse wave analysis machines [27, 28] which were validated against invasive measures of central BP [29]. More recently, the SphygmoCor XCEL estimates of central BP were found to correlate highly with invasively measured brachial and central BP [30]. The studies have shown that estimates of central BP and wave reflection are accurate and exceed criteria for repeatability and reliability [19, 31, 32].

Concurrently, patients wore an actiwatch and completed sleep diaries to document their sleep and wake times. Actigraphy data was analysed manually using Actiware (Phillips Actiware v.6, Respironics Inc, Murrysville PA, USA). The actiware options and settings were as follows: 1. Wake threshold selection was set at medium, 2. Immobile minutes for sleep onset and sleep end were set at 5 min. However, one patient demonstrated very frequent movements during sleep and for this study the immobile minutes setting was reduced to zero minutes in order for the software to recognise the period as sleep. Based on the results of the analysed actogram, the investigator then assigned a status of either wake or sleep to each blood pressure recording taken over the 24 h period.

Patients were on CPAP for a minimum of 4 weeks before repeat 24 h ABPM testing was performed. The settings for CPAP pressure were determined in either one of two ways depending on clinician preference. Either during a single overnight in-laboratory pressure titration sleep study where the pressure was manually titrated until obstructive events were abolished, or by placing the patient on auto-CPAP for a period of 2 weeks and then setting a fixed CPAP pressure based upon the 95th centile pressure applied during the preceding 2 weeks. Patients were reviewed by the CPAP therapist two weeks after commencement of CPAP for optimisation of therapy and at the end of the trial. Patients were reviewed more frequently if the CPAP therapist felt it was clinically indicated to help optimisation and acclimatisation to therapy.

Prior to statistical analysis, all 24 h-ABPM data that were deemed artefactual were identified and removed based on Staessen's criteria which included the following readings: systolic blood pressure  $> 240$  or  $< 50$  mmHg, diastolic blood pressure (DBP)  $> 140$  or  $< 40$  mmHg, heart rate (HR)  $> 150$  or  $< 40$  beats/min, and pulse pressure  $> 10\%$  of SBP [33]. As for the central indices, if the augmentation index (AIx) was  $\leq -80$ , or  $> 60$ , this was deemed artefactual and excluded along with the corresponding augmentation pressure (AP) and augmentation index corrected for heart rate (AIX@75) taken during that measurement. Central HR was used rather than peripheral HR as the method of collection is more accurate as the machine measures central HR from the length of the cardiac pulse, whereas peripheral HR is calculated by counting pulses during the oscillometric BP measurement. If peripheral HR and central HR differed by  $> 10$  beats per minute (bpm) then the central measurements were excluded as it indicated a poor quality waveform and only peripheral SBP and peripheral DBP were retained for those readings.

After artefactual readings were excluded, studies were reviewed and deemed unsuccessful if they contained less than 20 valid daytime readings or less than 7 valid night time readings as per European Society of Hypertension guidelines (see flowchart for numbers of excluded studies based on these criteria) [34].

### 2.3. Statistical analysis

Linear mixed models analyses were used to examine changes in peripheral blood pressure, central blood pressure and indices of wave reflection (AIx, AP) and PPA both before and after CPAP in sleep and wake. A paired *t*-test was used to compare the wake-sleep change in peripheral SBP and central SBP using mean wake to sleep differences for each patient. All statistical analyses were performed using IBM SPSS version 22.0 for Windows system (SPSS Inc., Chicago, IL). PPA was calculated as the % increase from central to peripheral pulse pressure as follows: ((Peripheral SBP–Peripheral DBP)–(Central SBP–Central DBP))/((Central SBP–Central DBP)) x 100. Non-dipping status was determined by ((Sleep SBP – Wake)/Wake SBP) x 100 ≤ 10%.

### 3. Results

36 patients were screened and were potentially eligible, 31 patients had successful baseline 24 h ABPM testing and 21 of these patients had successful testing post CPAP. The flow chart in Fig. 1 details exclusions and reasons.

Patient baseline characteristics are shown in Table 1. The baseline characteristics in the patients that went on to CPAP were similar (data not shown). The mean age was 45 ± 10 years and 77% were male. Overall the OSA was severe with mean AHI 58 ± 27 events/hr and patients were obese (mean BMI 32.3 ± 5.8 kg/m<sup>2</sup>). Hypertension was previously diagnosed in 32% of the patients and all were on antihypertensive therapy, however the mean office BP was within normal limits (<140/90) according to the Australian National Heart Foundation guideline [35]. Patients had an average nightly CPAP compliance of 5.12 ± 1.0 h with a residual AHI of 4.2 ± 3.3 events per hour.

#### 3.1. Changes in peripheral and central blood pressure and pulse pressure amplification indices between wake and sleep

Baseline peripheral and central blood pressure indices from wake to sleep are shown in Table 2. Both peripheral and central SBP and DBP and

**Table 1**  
Baseline characteristics of all patients<sup>a</sup>.

Characteristic	Measure
<b>Demographics (±SD)</b>	
Age, yr	45 ± 10
Male/female, n	24/7
BMI, kg/m <sup>2</sup>	32.3 ± 5.8
Waist circumference, cm	107.8 ± 10.6
Neck circumference, cm	41.9 ± 3.7
ESS	10 ± 5.4
Office SBP, mmHg	136 ± 10.7
Office DBP, mmHg	89 ± 9.5
<b>Ambulatory Blood Pressure</b>	
Non-dippers, n (%) <sup>b</sup>	7 (23)
Dippers, n (%) <sup>b</sup>	24 (77)
<b>Medical history, n (%)</b>	
Hypertension	10 (32)
Type 2 diabetes	0 (0)
Hypercholesterolemia	4 (13)
Stroke	0 (0)
Heart failure/Ischaemic heart disease	0 (0)
Current Smoker	2 (6)
Ex-smoker	12 (39)
<b>Anti-hypertensives at baseline, n (%)</b>	
Prescribed	10 (32)
1 antiHTN	5 (16)
2 antiHTN	4 (13)
3 antiHTN	1 (3)
<b>PSG values (±SD)</b>	
AHI, events/h	58 ± 27
ODI, events/h	49 ± 27
Min SaO <sub>2</sub> , %	75 ± 11

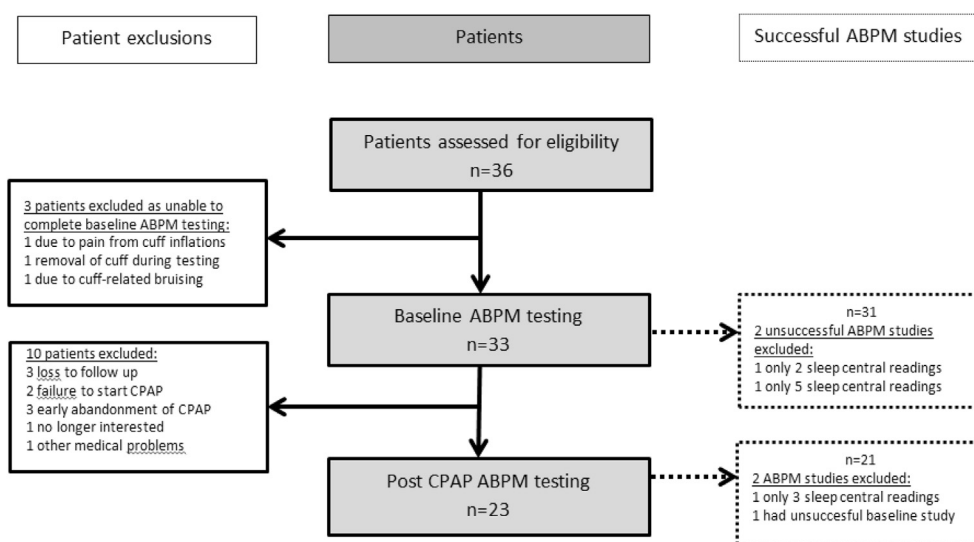
Plus-minus values are means ± standard deviation. BMI – Body-mass index (weight in kilograms divided by the square of the height in metres), ESS – Epworth Sleepiness Scale, PSG – Polysomnogram, AHI – Apnea-hypopnea index, ODI – Oxygen desaturation index, SaO<sub>2</sub> denotes oxygen saturation level as measured by pulse oximetry.

<sup>b</sup>PPA was calculated as ((P\_SBP – P\_DBP) – (C\_SBP – C\_DBP))/(C\_SBP – C\_DBP) x 100.

<sup>a</sup> Patients included those with successful baseline 24hABPM (n = 31).

<sup>b</sup> Non-dipping status was determined by ((Sleep SBP – Wake)/Wake SBP) x 100 ≤ 10%.

HR reduced significantly from wake to sleep demonstrating a diurnal dipping pattern (Fig. 2). Central SBP and DBP both reduced by equal amounts of 17 mmHg, however peripheral SBP dropped by 19 mmHg, whereas peripheral DBP dropped by 16 mmHg, effectively narrowing the peripheral pulse pressure in sleep. The reduction in central SBP was less



**Fig. 1. Study flowchart.** ABPM, ambulatory blood pressure monitoring; CPAP, Continuous positive airway pressure. Studies were deemed unsuccessful based on European Society of Hypertension guidelines.

**Table 2**Peripheral and central ambulatory blood pressure monitoring results in untreated patients n = 31<sup>a</sup>.

Variable	Wake	Sleep	Difference (sleep minus wake)	P value
P_SBP, mmHg	134.8 ± 2.0 (130.8–138.8)	115.6 ± 2.0 (111.5–119.7)	-19.2	<0.001
P_DBP, mmHg	83.8 ± 1.4 (80.9–86.6)	67.7 ± 1.5 (64.8–70.7)	-16.0	<0.001
C_SBP, mmHg	123.9 ± 1.8 (120.3–127.5)	106.9 ± 1.8 (103.2–110.5)	-17.1	<0.001
C_DBP, mmHg	85.3 ± 1.5 (82.3–88.4)	68.2 ± 1.5 (65.1–71.3)	-17.2	<0.001
C_HR, bpm	80.7 ± 1.6 (77.4–84.0)	66.9 ± 1.6 (63.6–70.2)	-13.8	<0.001
C_AP, mmHg	12.5 ± 0.7 (11.1–14.0)	14.7 ± 0.7 (13.1–16.2)	2.14	<0.001
C_AIx, %	31.0 ± 1.3 (28.3–33.7)	37.3 ± 1.4 (34.5–40.1)	6.3	<0.001
C_AIx 75, %	33.7 ± 1.4 (30.8–36.6)	33.4 ± 1.5 (30.4–36.4)	-0.319	0.661
P_PP, mmHg	51.0 ± 1.3 (48.4–53.7)	47.8 ± 1.4 (45.1–50.6)	-3.2	<0.001
C_PP, mmHg	38.7 ± 1.1 (36.5–40.9)	38.6 ± 1.1 (36.4–40.8)	0.124	0.795
PPA, % <sup>b</sup>	33.3 ± 1.1 (31.0–35.6)	22.6 ± 1.2 (20.1–25.0)	-10.7	<0.001

P\_SBP, Peripheral systolic blood pressure; P\_DBP, Peripheral diastolic blood pressure; C\_SBP, central systolic blood pressure; C\_DBP, central diastolic blood pressure; C\_HR, central heart rate; C\_AP, central augmentation pressure; C\_AIx, central augmentation index; C\_AIx 75, central augmentation index corrected for heart rate; P\_PP, peripheral pulse pressure, C\_PP, central pulse pressure; PPA, pulse pressure amplification.

<sup>a</sup> Data were analysed using linear mixed models; Values are mean ± standard error, (95% CI).

<sup>b</sup> PPA calculated as  $((P\_SBP - P\_DBP) - (C\_SBP - C\_DBP)) / (C\_SBP - C\_DBP) * 100$ .

than that of peripheral SBP (difference 2.3 mmHg,  $p < 0.001$ ). There was a large (~11%) reduction in PPA from wake to sleep due to the differential reductions in peripheral and central pulse pressure. In subgroup analyses, the reduction in PPA was no different in those with moderate versus severe OSA, or in those with HTN versus without HTN (data not shown).

### 3.2. Effects of CPAP on peripheral and central BP during wake and sleep

All central and peripheral BP indices before and after CPAP are presented in Table 3. The most notable changes occurred in wake measurements. Wake peripheral and central DBP and HR were reduced after treatment with CPAP whereas wake indices of wave reflection (C\_AP, C\_AIx, C\_AIx 75) increased after treatment. In contrast, sleep indices remained largely unchanged apart from a small drop in HR and a small increase in C\_AP. These CPAP associated changes during wakefulness subsequently altered the sleep related changes seen prior to CPAP. In particular, the wake related reduction in C\_DBP after CPAP significantly reduced the magnitude of the subsequent sleep related dip that was present before CPAP by 2.4 mmHg ( $p = 0.016$ ). Similarly, the wake related increase in arterial stiffness with CPAP attenuated the magnitude of the sleep related rise in C\_AP by 2.2 mmHg ( $p < 0.001$ ) and resulted in an absolute reduction in sleep AIx\_75 by 4.6% ( $p < 0.001$ ). Finally, the nocturnal fall in PPA (~9%) after CPAP was attenuated by 3.3% ( $p < 0.004$ ).

## 4. Discussion

This is the first study to demonstrate the diurnal pattern of central blood pressure (BP) and pulse pressure amplification (PPA) in patients with moderate to severe OSA. We also describe for the first time in a

small number of patients, the changes in 24 h central BP and PPA after CPAP treatment. We found that similar to peripheral BP, central BP dips during sleep. However, systolic and diastolic BP reduced by different amounts in sleep peripherally and centrally, causing a reduction in peripheral pulse pressure whilst there was no change in the central pulse pressure. This led to a reduction in PPA overnight. This attenuation in PPA was consistent with our findings of an increase in wave reflection during sleep. These results highlight the fact that peripheral BP and central BP and its components behave differently. With CPAP, this attenuation was unexpectedly diluted— not because of a hypothesised decrease in wave reflection during sleep, but instead because of a paradoxical increase during wakefulness.

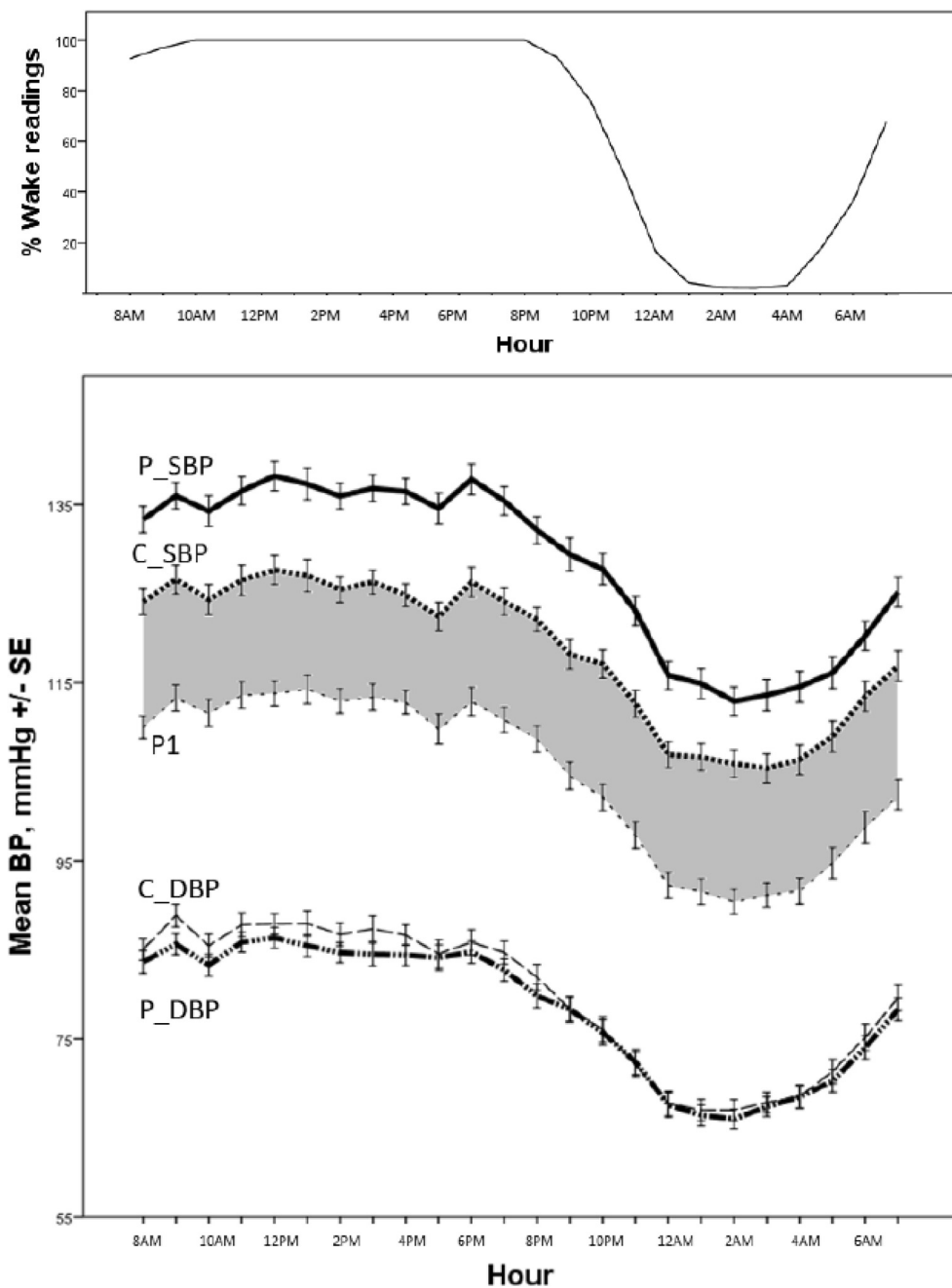
Our 24 h CBP and PPA findings in untreated OSA patients are similar to other very recent studies in hypertensive and normotensive populations without OSA [19,36–38]. However to date, only one of these studies explored central BP data with the same Oscar 2 device used in our study [19]. This study in 40 healthy participants demonstrated good-to-excellent inter-day reliability and validity of the Oscar 2 device by comparing static measures with ambulatory values and by repeating ambulatory measures in individuals at different time points. Similar to our study in OSA, they found in healthy participants that the magnitude of drop during the night in central SBP was attenuated as compared to peripheral SBP. The absolute reductions in peripheral and central SBP were comparable to our study (20 mmHg and 15 mmHg respectively, compared to 19 mmHg and 17 mmHg in our study).

For any given peripheral SBP, the central SBP will be lower and the magnitude of the difference is measured as pulse pressure amplification. Hence pulse pressure amplification refers to the phenomenon whereby pulse pressure (or the difference between SBP and DBP) increases when moving distally from the heart to the peripheral arterial tree. This amplification in healthy people represents normal physiology, however factors such as aging, and CV risk factors such as hypertension, diabetes mellitus and established CV disease are associated with reduced PPA [21] – which is thought to be chiefly due to a relative increase in aortic SBP as a consequence of increased wave reflection [39, 40]. The development of ambulatory devices that measure central and peripheral BP has revealed that PPA, like peripheral SBP, also dips nocturnally [36–38, 41]. To the best of our knowledge, we are the first to report on 24 h PPA in patients with OSA, finding that PPA reduced by 10% from wake to sleep. Consistent with previous studies in non-OSA groups, we have shown that PPA dipping occurs because of a greater sleep reduction in peripheral pulse pressure as compared to central pulse pressure [36–38, 41].

With regards to wave reflection (C\_AP, C\_AIx), several 24 h studies in hypertensives and normotensives have found that this increases at night [38, 41, 42] and this likely explains the reduction in PPA during sleep. In our patients with OSA, we found a sleep-related rise of 2 mmHg in augmentation pressure and 6% in augmentation index but this effect was negated when corrected for heart rate (C\_AIx 75). Only one other study has performed ambulatory measures of AIx in OSA (albeit with a different device and the authors did not report on corresponding central blood pressures) and found no change from day to night [43]. Interestingly, this study also found that control subjects without OSA had a significant drop in AIx from day to night. This contrasts with another much larger study of 500 non-OSA patients (using the same device) which showed a rise in AIx [41]. It is unclear whether the device used had undergone any formal validation to assess the accuracy of the AIx derivation. Certainly, the only directly comparable study to ours, using the validated Oscar 2 (which also measures central BP) found a 4 mmHg rise in augmentation pressure, 9% rise in AIx and 3% rise in AIx corrected for HR from daytime to nighttime [19]. These changes in young healthy controls are approximately two-fold greater than the changes we observed in our OSA patients and leads us to speculate that the sleep-related increase in systemic arterial stiffness (as measured by augmentation pressure and augmentation index), is likely to represent normal physiology.

The mechanisms underpinning the drop in PPA and increase in wave reflection which have been shown across studies are not fully





**Fig. 2. Ambulatory peripheral and central blood pressure profile over 24 h in untreated patients with OSA.** The top panel depicts the percentage of blood pressure readings scored as wake in all patients at any given hour across the 24 h period based on actigraphy analysis. The bottom panel depicts the overall mean blood pressure values every hour across the 24 h. The shaded area schematically represents augmentation pressure and P1 represents unaugmented central systolic pressure. P\_SBP, Peripheral systolic blood pressure; P\_DBP, Peripheral diastolic blood pressure; C\_SBP, central systolic blood pressure; C\_DBP, central diastolic blood pressure.

understood. It could be argued that these overnight changes could be attributed to changes in posture given the findings of a well-designed study which performed static measurements in awake individuals in the sitting and supine position [44]. The study found that in the recumbent (supine) position, PPA was reduced, whilst measures of wave reflection (augmentation pressure and AIx) all increased [44]. However the absolute sitting-supine change in PPA was less than 4% as compared to nearly ~11% in our OSA patients and ~9% in the aforementioned healthy control study [19]. Hence, although recumbent posture might account for some of the overnight change, there are likely to be other mechanisms involved. In this context, the bulk of the increase in augmentation pressure in our study appeared to occur from midnight when most participants were (according to actigraphy) asleep (Fig. 2 top panel and shaded area – bottom panel), suggesting that a change associated with sleep itself is a likely contributing factor. These changes might include a reduction in sympathetic tone which could impact on

both vascular tone and heart rate which both impact on the magnitude of wave reflection.

In the context of changes in heart rate with sleep, these likely contribute to both the wake-sleep PPA and AIx changes. It has already been established in studies using static measures that PPA and AIx are directly and inversely related to HR, respectively [39, 40]. In support of this, our analysis found a strong relationship between the wake to sleep change in HR and PPA ( $r = 0.648$ ,  $p < 0.001$ , Fig. 3) in keeping with other 24 h study findings [37, 41]. This reduction in HR during sleep increases the duration of ventricular ejection, thereby exposing the left ventricle to a greater proportion of the reflected wave from the lower body. This acts to augment the forward pressure wave in systole thereby increasing augmentation pressure and central systolic blood pressure [39, 40]. This potentially accounts for the attenuated nocturnal dip in central SBP as compared to peripheral SBP. In Fig. 2, we demonstrate schematically this increase in augmentation pressure (shaded area) in

**Table 3**Peripheral and central ambulatory blood pressure monitoring results in patients before after treatment with CPAP therapy, n = 21<sup>a</sup>.

Variable	Wake		Change	P value	Sleep		Change	P value
	Before CPAP	After CPAP			Before CPAP	After CPAP		
P_SBP, mmHg	133.0 ± 1.6 (129.6–136.4)	133.4 ± 1.6 (130.0–136.8)	0.414	0.557	112.2 ± 2.0 (108.0–116.4)	112.2 ± 2.0 (108.1–116.4)	0.036	0.968
P_DBP, mmHg	84.3 ± 1.3 (81.5–87.1)	82.0 ± 1.3 (79.2–84.4)	-2.287	<0.001	66.7 ± 1.4 (63.7–69.7)	66.2 ± 1.4 (63.2–69.2)	-0.447	0.518
C_SBP, mmHg	122.5 ± 1.6 (119.3–125.7)	123.0 ± 1.6 (119.8–126.2)	0.492	0.458	104.2 ± 1.8 (100.4–108.0)	105.6 ± 1.8 (101.8–109.4)	1.428	0.113
C_DBP, mmHg	85.8 ± 1.4 (83.0–88.6)	83.1 ± 1.4 (80.3–85.9)	-2.640	<0.001	67.4 ± 1.5 (64.3–70.4)	67.2 ± 1.5 (64.1–70.3)	-0.188	0.799
C_HR, bpm	80.2 ± 2.0 (76.0–84.3)	77.2 ± 1.9 (73.0–81.4)	-2.931	<0.001	66.5 ± 1.5 (63.3–69.7)	63.4 ± 1.5 (60.2–66.6)	-3.108	<0.001
C_AP, mmHg	11.2 ± 1.0 (9.2–13.2)	14.4 ± 1.0 (12.4–16.4)	3.146	<0.001	13.8 ± 0.7 (12.3–15.2)	14.8 ± 0.7 (13.3–16.2)	1.028	0.014
C_AIx, %	29.1 ± 1.7 (25.5–32.6)	34.6 ± 1.7 (31.0–38.2)	5.554	<0.001	36.7 ± 1.4 (33.8–39.6)	37.9 ± 1.4 (35.0–40.8)	1.16	0.122
C_AIx 75, %	31.5 ± 1.6 (28.1–34.9)	35.7 ± 1.6 (32.4–39.1)	4.283	<0.001	32.7 ± 1.8 (28.9–36.5)	32.4 ± 1.8 (28.7–36.2)	-0.283	0.713
P_PP, mmHg	48.7 ± 1.2 (46.3–51.1)	51.4 ± 1.2 (49.0–53.8)	2.701	<0.001	45.5 ± 1.1 (43.2–47.9)	46.0 ± 1.2 (43.6–48.4)	0.469	0.488
C_PP, mmHg	36.7 ± 1.2 (34.3–39.1)	39.8 ± 1.2 (37.4–42.3)	3.126	<0.001	36.8 ± 0.9 (34.9–38.7)	38.5 ± 0.9 (36.6–40.4)	1.695	0.003
PPA, %	34.3 ± 1.6 (31.0–37.5)	28.9 ± 1.6 (25.7–32.2)	-5.338	<0.001	22.4 ± 0.9 (20.5–24.3)	20.2 ± 0.9 (18.3–22.1)	-2.185	<0.001

<sup>a</sup> Data were analysed using linear mixed models; Values are mean ± standard error (95% CI); P\_SBP, Peripheral systolic blood pressure; P\_DBP, Peripheral diastolic blood pressure; C\_SBP, central systolic blood pressure; C\_DBP, central diastolic blood pressure; C\_HR, central heart rate; C\_AP, central augmentation pressure; C\_AIx, central augmentation index; C\_AIx 75, central augmentation index corrected for heart rate; P\_PP, peripheral pulse pressure, C\_PP, central pulse pressure; PPA, pulse pressure amplification; PPA calculated as  $((P\_SBP - P\_DBP) - (C\_SBP - C\_DBP)) / (C\_SBP - C\_DBP) * 100$ .

parallel with the dampening of the central SBP dip during the night.

Multiple meta-analyses of RCTs have demonstrated that CPAP results in a modest reduction in SBP of approximately 2–3 mmHg in patients with OSA and HTN [45,46,47–49]. Only one study has looked at the effect of CPAP on 24 h-ABPM in normotensive OSA patients and found that whilst the SBP was unchanged, 24 h DBP and daytime DBP reduced significantly by 1.38 mmHg and 1.39 mmHg respectively [50]. Similarly, in our mostly normotensive patients, treatment with CPAP resulted in a reduction in wake peripheral and central DBP as well as wake and sleep HR. We had postulated that following elimination of OSA with CPAP, there would also be a reduction in wave reflection across both the wake and sleep periods. Instead there was an increase during the wake period after CPAP. Whilst the cause for the wake-related increase is unclear, it did not carry through to the subsequent sleep period. Although highly speculative, this lack of absolute change in the magnitude of wave reflection during sleep may represent two opposing effects. The reduction in sympathetic activity with CPAP could potentially decrease arterial stiffness thereby reducing augmentation pressure. In contrast, a reduction in sympathetic activity would also lower heart rate, which would increase augmentation pressure. The combined effects would be neutral.

The increase in wave reflection (AP, AIX and CAIX75) during wakefulness after CPAP is contrary to the findings from other studies using static office-based measurements which have consistently shown a reduction [51, 52]. Similarly, an attenuated PPA dip with CPAP is difficult to explain seeing as the expected effects of treatment overnight such as a reduction in sympathetic activity, and reduction in left ventricular afterload, should all theoretically cause a further reduction in sleep PPA. Interestingly, a large cross-sectional 24 h study of patients with suspected or established hypertension paradoxically found one of the factors associated with less PPA dipping at night was the use of antihypertensives [41]. Also of interest is that beta blockers, unlike other anti-hypertensives, have been shown to decrease PPA, by having a much more marked effect on lowering peripheral BP as compared to central BP [53]. Clearly the impact of blood pressure lowering treatments on the haemodynamic changes between wake and sleep are complex and not yet fully understood. Ultimately, although the effect of CPAP involved only a relatively small sample of patients, we did find in secondary analyses (results not shown) that the increase in wake AP after CPAP was a consistent finding in 19 of the 21 patients studied. Nevertheless these effects need to be replicated with a larger study and appropriate control group.

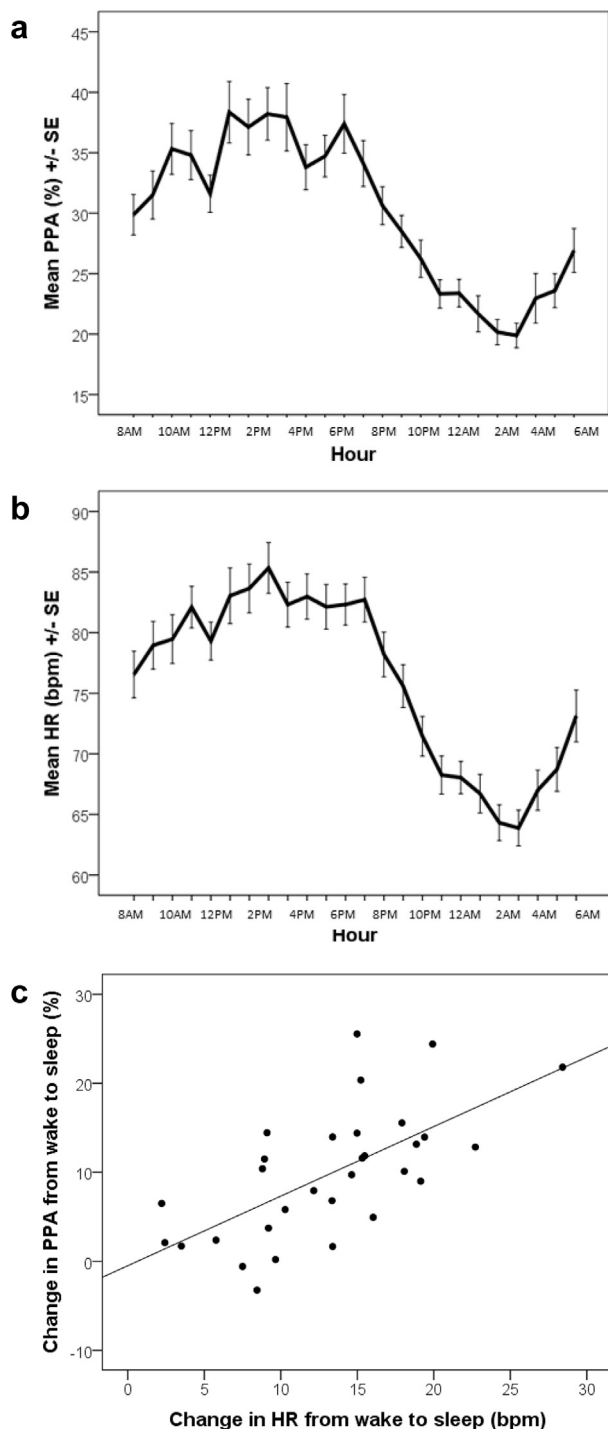
Overall, whilst this study is novel in exploring central hemodynamic changes across the sleep-wake cycle in OSA, it is limited by its

observational design and small sample size. It is further limited by an even smaller sample of patients completing the CPAP follow up. Secondly, a non-OSA comparator group would have strengthened the study, as well as a sham CPAP arm to confirm that the changes were related to CPAP use. Given the lack of a control group, we compared our baseline values to a study with healthy participants (albeit of a younger demographic with a greater proportion of females) that used the same device. Finally, despite the severity of the underlying OSA, the group were largely normotensive and it remains to be determined whether similar wake-sleep changes in central BP and PP amplification would occur in a hypertensive OSA group and whether CPAP treatment would differentially alter these measures. The strengths of this study were that we utilised gold standard in-lab polysomnography for accurate identification of our patients, and more importantly, we utilised individualised wake and sleep times for each patient by using actigraphy as well as sleep diaries. This means that measures of sleep-wake changes are technically more accurate and this has not been replicated in any of the other 24 h central BP studies. Lastly, we used a blood pressure device that was validated not only for central BP readings but also for AIX.

New ambulatory technology has allowed us to describe for the first time the diurnal variation of central blood pressure and pulse pressure amplification in OSA, a population at risk of poor cardiovascular outcomes. There is emerging data to suggest that these hemodynamic findings may be better predictors of target organ damage and future cardiovascular risk than peripheral brachial measurements. Central blood pressure is importantly, a more accurate representation of end-organ BP exposure including the heart and kidneys. Furthermore, central BP changes differently to peripheral blood pressure during sleep and in response to different anti-hypertensives. This study paves the way for future research in the hypertensive OSA population, specifically examining the effects of CPAP on central blood pressure and the differential therapeutic and chronotherapeutic effects of various classes of anti-hypertensives.

#### Statement of significance

Advances in technology now allow the non-invasive measurement of 24 h ambulatory central blood pressure (BP) and pulse pressure amplification (PPA). In this study we characterise for the first time the diurnal profile of central BP and PPA in patients with obstructive sleep apnoea (OSA). We found that central and peripheral BP behaved differently across the 24 h. During sleep, peripheral pulse pressure (PP) narrowed, whereas central PP did not, causing a significant reduction in PPA



**Fig. 3.** 24-hour association between PPA and HR in untreated OSA (a) Pulse pressure amplification (b) central HR (c) correlation between change in PPA from wake to sleep versus change in HR from wake to sleep.

overnight. After treatment with CPAP, the PPA reduction overnight was attenuated. This novel study provides a new direction for future research to better understand arterial haemodynamics and cardiovascular risk stratification in OSA, a group in which hypertension is difficult to control.

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